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Recommendations for the prevention of healthcare-associated infections in nursing homes

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ABSTRACT

Nursing homes (NH) conceptually should look as much like a home as possible. However NH have unquestionable similarities with a nosocomium as they are places where many patients with underlying diseases and comorbidities accumulate. There is evidence of transmission of microorganisms between residents and between residents and caregivers.

We have not found any recommendations specifically aimed at the prevention of nosocomial infections in NH by the major Public Health Agencies and, therefore, the Health Sciences Foundation (Fundación de Ciencias de la Salud) has convened a series of experts and 14 Spanish scientific societies to discuss recommendations that could guide NH personnel in establishing written programs for the control and reduction of these infections. The present document is the result of these deliberations and contains suggestions for establishing such control programs on a voluntary and flexible basis in NH. We also hope that the document can help the health authorities to encourage this control activity in the different territorial areas of Spain. In our opinion, it is necessary to draw up a written plan and establish the figure of a coordinator or person responsible for implementing these projects. The document includes measures to be implemented and ways of quantifying the reality of different problems and of monitoring the impact of the measures established.

Keywords: Nosocomial infection, nursing homes, respiratory infection, urinary tract infection, skin and soft tissue infection, environmental hygiene measures, incentive to use vaccines

Recomendaciones para la prevención de infecciones en residencias para mayores

RESUMEN

Las residencias de ancianos (NH) aunque conceptualmente deberían parecerse lo más posible a un hogar, tienen indudables similitudes con un nosocomio ya que son lugares donde se acumulan muchos pacientes con enfermedades de base y comorbilidades y donde la transmisión de microorganismos entre residentes y entre residentes y cuidadores es frecuente. No hemos encontrado recomendaciones específicamente dirigidas a la prevención de las infecciones nosocomiales en NH por par-

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te de las principales Agencias de Salud Pública y, por ello, la Fundación de Ciencias de la Salud ha convocado a una serie de expertos y a 14 sociedades científicas españolas para debatir recomendaciones que puedan orientar al personal de las NH en el establecimiento de programas escritos para el control y reducción de estas infecciones. El presente documento es el resultado de estas deliberaciones y contiene sugerencias para establecer dichos programas de control de forma voluntaria y flexible. También esperamos que el documento pueda ayudar a las autoridades sanitarias a fomentar esta actividad de control en los distintos ámbitos territoriales de España. En nuestra opinión, es necesario elaborar un plan por escrito y establecer la figura de un coordinador o responsable de la ejecución de estos proyectos. El documento incluye las medidas a implantar y las formas de cuantificar la realidad de los diferentes problemas y de monitorizar el impacto de las medidas establecidas.

Palabras clave: Infección nosocomial, residencias de ancianos, infección respiratoria, infección del tracto urinario, infección de piel y tejidos blandos, medidas de higiene ambiental, incentivo al uso de vacunas.

INTRODUCTION

Nursing homes are one of the care services included in the Spanish System for Autonomy and Care for Dependency (SAAD in Spanish). They logically try to reproduce living conditions for their inhabitants as close as possible to those at home, favouring human contact with other residents, family members and visitors.

However, they are places favouring the transmission of infections, as people with frequent and important underlying diseases live in close proximity to each other, sharing caregivers in a common habitat thus hindering the existence of control and isolation zones.

We know a lot about infection prevention measures in hospitals and healthcare centres, but we know very little about infection prevention in smaller institutions with fewer resources for this purpose, such as nursing homes.

We are not currently aware of any regional or national programme on healthcare-associated infection (HAI) prevention specific to nursing homes, so we have developed a practical set of recommendations aimed at the prevention and control of infection in nursing homes.

For this reason, the Board of Trustees of the Health Sciences Foundation conducted a review of the literature on the prevention of infection in nursing homes in our country and on the existing indicators used to monitor this process. The topics were distributed among a multidisciplinary group of experts, including the views of scientific societies, patient associations, the media, government officials, geriatricians, infectious disease specialists, microbiologists and other specialists. The lines that follow are the results of multiple meetings and discussions.

MATERIAL AND METHODS

Two of the authors conducted a systematic literature search in PubMed using keywords: Infection Prevention Control, Nursing Homes, Long Term Care Facilities, Health Care Related Infection; as well as in official documents of the Health Departments of the Autonomous Communities, the Ministry of Health, the World Health Organisation (WHO) and the European Centre for Diseases Control (eCDC).

With the data obtained, a first document with recommendations was drawn up for subsequent discussion by a multidisciplinary drafting team, which was reviewed by the rest of the authors representing the different scientific societies and organisations that endorse the document.

DEFINITION AND CLASSIFICATION OF NURSING HOMES

Some characteristics of nursing homes and the people who live in them. Nursing homes are establishments intended for the temporary or permanent accommodation of dependent individuals, with services and intervention programmes adapted to the needs of the people being cared for, aimed at achieving a better quality of life and promoting their personal autonomy.

They represent a diverse group of social and health care settings serving people of various ages and functional abilities and providing an increasingly wide range of services with varying degrees of care.

In terms of infection control, some characteristics of these centres need to be taken into account:

1. People living in nursing homes accumulate a high number of chronic diseases: the most recent study in Spain on comorbidity and resource use of people living in nursing homes shows a very significant increase in morbidity in the last decade [1]. Specifically, using average figures, the age was 87 years, there were 7 chronic diseases per person and 11 pharmacological active ingredients were consumed per person, with a high yearly mortality (20.4%). Compared to the non-institutionalised elderly population they had a higher multimorbidity rate (15.2% vs. 4.2%), with a higher number of chronic diseases, especially dementia (46.5% vs. 4.6%).

2. Hospital visits by these people are very frequent: compared to the non-institutionalised elderly population, this population has a higher number of hospital admissions (47.6% vs. 27.7%), a higher number of admissions to medium-stay hospitals (27.8% vs. 7.4%) and a longer hospital stay, once admitted (10 days vs. 7.2 days).

3. Staff and resident ratios are small and directed only to care and not to infection prevention. A recent study by the Spanish Society of Geriatrics and Gerontology (SEGG) on the regulations affecting nursing homes in Spain [2], highlights the existence of very tight staffing ratios mainly aimed at general care, with little emphasis on prevention and control of intercurrent diseases and infection in these centres. As an example, the average time spent with a geriatric carer per resident ranges from 43 minutes to 83 minutes and with a nurse from 5 to 22 minutes per day.

These figures make it very difficult to establish ambitious infection control programmes and encourage indiscriminate transfer to the referral hospital, where the risk of healthcare-associated infection (HAI) is elevated.

4. The health care provided in nursing homes depends on the national health system in Spain and the health services of each autonomous community, as stipulated in all regulations. This leads to the medical management of these people with such a high complexity and burden of chronic diseases falling on the primary care referral and, in the most severe cases, on the hospitals. Instead, care is episodic, with difficult or non-existent coordination between social and health services. This also means a loss of clinical information that is vital for infection control should infection occur.

5. Only a few autonomous communities regulate the presence of a clinical professional (usually a nurse) as the person responsible for the hygienic-health care processes of these people.

Currently, the model is in a phase of change towards smaller nursing homes, with a closer, more person-centred model of care. The recent agreement reached in 2022 between the Autonomous Communities and the State favours a model of residential care based on the following principles [3]:

a. Smaller centres (maximum 75, 90 or 120 places). The classification proposed in these recommendations already covers this standard.

b. Model of person-centred care, with respect for the preferences and participation of the family in an environment free of physical and chemical restraints.

c. Very modest increase in staffing ratios.

d. Health care remains in the hands of the health services, yet there is no regulation on how to do this.

The current model poses the difficult challenge of maintaining environments that are homey, familiar and open to the community, as well as respectful of people's dignity and infection control (e.g. isolation is an enormous assault on their mental, functional and emotional balance and should be an exceptional measure).

Classification of nursing homes for infection control: a proposal. The Institute for the Elderly and Social Services (IMSERSO) still classifies nursing homes into residences for the elderly, assisted living and mixed residences. But this is a classification that is clearly in disuse nowadays and there is a tendency to speak of nursing homes in general, regardless of their size and variety of services.

The classification of nursing homes according to the greater or lesser presence of professionals dedicated to carrying out therapeutic work such as convalescence or rehabilitation stays is also found in other countries [4].

In any case, these classifications shed very little light on how to grade the risk of transmission of infection, so a self-developed classification has been proposed in these consensus recommendations. This classification is detailed below.

Table 1 System for classifying nursing homes according to their risk of infection.

INDICATORS		Points
Number of residents	<75	0
	75-120	1
	>120	2
Rooms (>65%)	Single	0
	Double	1
	≥ 3	2
Median of the Barthel score of the individual residents.	>55 pts Barthel Scale	0
	35-55 pts Barthel Scale	1
	<35 pts Barthel Scale	2
% residents with a bladder catheter	< 10%	0
	11-25%	1
	>25%	2
Nurses	Full Time	0
	Part-time	1
	One-time Visit	2
Medical Staff	Full Time	0
	Part-time	1
	One-time Visit	2
Infection Prevention Plan (vaccination protocols, use of antibiotics, general measures, staff training)	Total and ongoing	0
	Partial	1
	Not available	2
Possibility of room isolation	Total	0
	Partial	1
	Not available	2
Is there hospital-medical referral and direct/telephonic hospital or community pharmacy?	Total	0
	Partial	1
	Not available	2
Proportion of staff (full-time) in direct first level care	>0.43	0
	Between 0.31 and 0.43	1
	<0.31	2

Classification of the risk of infection in nursing homes. We know that in social and healthcare centres, due to their characteristics, the profile of the elderly who reside in them, the existence of multiple underlying conditions, polymedication and many other variables, there is a higher prevalence of infections. In order to be able to quantify the risk of HAI and then offer different recommendations, we propose a classification system based on a series of variables chosen at our discretion that we believe can serve as indicators of the risk of HAI in nursing homes (Table 1).

We are aware of the limitations that this classification may have, but it can give us a rough idea of what we want to know. These variables could be:

- Number of residents: the greater overcrowding of spaces may favour the transmission of infections.
- Number of single/double/triple rooms: sharing rooms favours possible transmission.
- Degree of dependency assessed by the Barthel scale: many of the items assessed by the Barthel scale have a lot to do with factors that may predispose to infection (incontinence, toileting, immobility). We understand that the greater the dependency, the greater the risk. We distinguish between mild, moderate and severe.
- Proportion of residents (%) with bladder catheters or invasive devices in general: all these devices are known to be a potential source of infections.
- Medical staff, pharmacists and nursing professionals in the centres, as reference personnel who contribute to prevention, detection and treatment in the case of infectious processes.
- Existence or lack of infection prevention plans: vaccination protocols, protocols for the use of antibiotics for the most prevalent infections, protocols for general infection prevention measures, staff training.
- Possibility of isolation: assess whether it is possible, if necessary, to keep affected residents isolated from contact with other healthy residents, while maintaining the care they need and taking all possible precautions with regard to the staff attending to them.
- Existence of nursing home-primary care-hospital referral: there is a relationship and contact with the specialist in the hospital for the joint assessment of cases.
- Ratio of first level direct care staff (assistants/geriatric carers): in relation to the number of assistants caring for residents. The requirements in the different communities are very different and vary according to the type of residents in relation to their degree of dependency. According to the new accreditation criteria prepared by the Ministry of Social Rights (Accreditation and Quality Agreement 28/06/2022) this ratio starts from 0.31 to 0.43 for the coming years as a minimum requirement for centres with a majority of dependent residents (grade II/III).

With these parameters we summarise in Table 1 a point system that could roughly classify nursing homes according to their risk of HAI into:

- Low risk of HAI: between 0 and 5 points.
- Medium risk of HAI: between 6 and 10 points.
- High risk of HAI: between 11 and 20 points.

RECOMMENDATIONS FOR ACTION

The following are some recommendations for establishing the basis for an infection control programme in nursing homes.

It is recommended to developed a programme for the prevention and control of HAI in nursing homes at all levels. The main functions of the PPCIR are to prevent infection of residents through surveillance and early diagnosis activities, and to ensure that measures are in place to prevent the acquisition of infections and the transmission of pathogenic micro-organisms. To achieve these objectives in a cost-effective manner, we believe that all nursing homes should have a written plan with an active and effective programme throughout the organisation and its implementation should be supported continuously by the management.

A key component is to have written infection control protocols (including those related to environmental hygiene), and implement them so as to detect, contain and prevent the transmission of potential pathogens. Infection control programmes should be tailored to the type of facility, facility layout (including isolation facilities), risk factors among residents and available resources.

It is advisable to designate one person as coordinator. We believe that in order to guarantee compliance with any protocol or PPCIR, it is preferable for it to be led by a healthcare professional who has the support and recognition of the centre's management and who is a point of reference for the healthcare team to coordinate activities and improve communication with the rest of the professionals, both from the centre itself and from the Public Health Service.

Regarding the person assigned as responsible, it is desirable (although not essential) that he/she has knowledge of infectious disease control and management (clinical manifestations, mechanisms of transmission and spread, and prevention measures); leadership and communication skills, as well as teamwork skills. This person is the one who must transmit all information to the rest of the professionals in the institution, as well as to the residents and their relatives, ensuring that all necessary infection prevention measures are carried out. On the other hand, this person is the one who must inform the Public Health System of relevant events and also the Primary Care physician responsible for the care at the nursing home, as well as the Specialised Geriatric Hospital Services. This work is essential for the prevention of any communicable disease; as well as to quickly implement the contingency plan, and/or isolation precautions and avoid transmission to the rest of the residents, workers, and visitors.

It is recommended that an annual education and training plan for healthcare workers be drawn up. Continuous training of workers is an aspect that certainly deserves a great deal of attention. We believe that successful implementation of infection prevention programmes in nursing homes should have very specific objectives and include aspects of training for both staff and residents. The following is a list of recommendations which, although they are not the only ones that exist, are what we consider to be the minimum necessary for the development of an infection prevention and control

plan in nursing homes.

There should be a protocol for environmental prevention measures. We would particularly like to stress that except in the circumstances of immunocompromised residents, air quality control measures cannot be extrapolated to those carried out in hospital environments. We have not found any specific legislation for nursing homes in terms of air quality monitoring.

In some Autonomous Communities, there are regulations that establish the environmental cleanliness measures that all centres, in addition to complying with the general legislation in force on hygiene and health, must guarantee. These recommendations are summarised below.

- General and permanent cleaning of the building and its dependencies, especially those under heavy use, as well as disinfection using detergents with disinfectant capacity (chlorinated detergents, quaternary ammonium compounds, etc.). Disinfectants for sanitary use or products accepted by the Spanish Agency for Medicines and Medical Devices (AEMPS) for application in the sanitary field shall preferably be used.
- Annual insect and rat extermination, or as often as circumstances require.
- Cleaning and disinfection of crockery and cutlery after use, by means of automatic hot washing, as well as other commonly used instruments.
- Suitable space should be available for the temporary storage of waste in closed bins (intermediate storage).

It is recommended to have written instructions for a hand hygiene plan for staff and visitors. Hand hygiene is one of the most important infection control measures. Residents should be cared for with clean hands and the lowest microbial load to avoid infections and the transmission of potentially pathogenic microorganisms. Each nursing home needs to have a plan in place to promote proper hand hygiene for workers, detailing when, how and with which products to perform hand hygiene. In addition, it must ensure the availability of products and devices, as well as the regular training and education of workers.

Hand hygiene of workers should preferably be carried out with hydroalcoholic solutions, if the hands are not visibly soiled. The facility should be equipped with an adequate supply of alcohol-based products at the main points of resident care or provide individual flasks for staff use. If this is not the case, washing with soap and water should be carried out. The hand hygiene technique established by the WHO should always be performed and the WHO 5 Moments for Hand Hygiene should be followed in the nursing home [5].

Different complementary strategies can be used to improve compliance with this basic hygiene measure. One is the monitoring of compliance through direct observation as all hand hygiene opportunities can be explicitly accounted for, those who do not practice hand hygiene can be identified and the reasons for non-compliance explored. The observation should be carried out by a healthcare professional previously trained in the subject [6]. Another indirect and less costly measure of compliance is the monitoring of consumption (quarterly, yearly, etc.) of hydro-alcoholic and/or soap solutions, and of course it is good practice to have dispensers in rooms, common areas such as gyms, consulting rooms, bathrooms and living spaces.

It is advisable to have a written document on the proper use of gloves. Common, disposable, single-use, non-sterile gloves are a protective measure for the worker. However, the use of such gloves has been identified as a barrier to proper hand hygiene and as a factor in the spread of micro-organisms.

Therefore, gloves should only be used when contact with non-intact skin, blood or body fluids such as secretions, urine, faeces, etc. is anticipated. When contact is to be made with clean whole skin or with objects that are not stained with the above liquids, gloves need not be worn.

It is desirable to have a document of recommendations for the prevention of both catheter-associated (CA-UTI) and non-catheter-associated urinary tract infection (UTI)

Residents without bladder catheters

Although the management of UTI is not the main focus of this document, we wish to emphasise that more than 20% of older people may have asymptomatic bacteriuria, which at some point could be mistaken for UTI. Current management guidelines do not recommend the indiscriminate screening for bacteriuria as a marker of infection in residents without manifestations directly attributable to the urinary tract, nor the use of urine strips as a diagnostic method for UTI. From a preventive point of view, hygiene and toileting of continent residents is very important in this group of residents, as well as frequent nappy changing and perineal hygiene in incontinent residents.

Residents with temporary urinary catheters

Below, we highlight some of the basic strategies for preventing CA-UTIs:

- Insert catheters only for appropriate indications.
- Leave catheters in place only as long as necessary.
- Ensure that only duly trained persons insert and maintain catheters.
- Insert catheters using aseptic technique and sterile equipment. Extreme hand hygiene measures before putting on gloves and after removing them.
- After aseptic insertion, maintain a closed drainage system.
- Maintain unobstructed urine flow.

Residents with long term indwelling bladder catheters

To reduce the incidence and duration of catheterisation, it is important to assess and communicate the presence of a urinary catheter to the medical team and reassess the indication periodically. A simple continuous quality improvement

Table 2 Norton Scale

General physical condition	Mental condition	Activity	Mobility	Incontinence	Points
Very bad	Stuporous/ coma	Bedbound	Immobile	Urinary and faecal	1
Poor	Confused	Chairbound	Very limited	Urinary or faecal	2
Fair	Apathetic	Walks with help	Slightly impaired	Occasional	3
Good	Alert	Ambulant	Full	None	4

Adapted from Norton, D: Calculating the risk: Reflections on the Norton scale. Decubitus 2(3):24–31, 1989.

programme based on nurses asking physicians if continued catheterisation is necessary significantly reduces the duration of urinary catheterisation as well as the rate of catheter-associated urinary tract infections.

For further information, please consult the guidelines for the prevention and management of catheter-associated urinary tract infection on the European Centre for Disease Prevention and Control (ECDC) website [7].

It is advisable to have a protocol with recommendations for the prevention of respiratory infection. Outbreaks of respiratory infections occur in all residences throughout the year, but are most frequent from autumn to early spring. Such outbreaks can cause considerable morbidity and mortality, so we believe it is imperative that every nursing home, regardless of level, should have in place a set of written policies and procedures related to outbreaks of respiratory infections, including early detection of infection, staff and resident education, and vaccination requirements.

We believe that daily active surveillance is the most effective way to prevent and detect respiratory infections, which involves staff identifying symptoms of respiratory infection. Although it is beyond the scope of this document, we wish to recommend the use of self-diagnostic tests in people with new-onset respiratory manifestations. As the sensitivity of these tests does not allow the diagnosis to be excluded, it is recommended that residents with clinical manifestations avoid contact with other residents and that visitors wear masks. While a negative result does not exclude the diagnosis, a positive result has a high positive predictive value.

Some of the official recommendations currently available can be consulted in detail [8, 9]. At the core of these recommendations will be the isolation of infected residents, reduction of visits and vaccination policy.

There should be a system of regular assessment of the vaccination status of residents and workers by the nursing homes. Vaccination is one of the most important cost-effective strategies for the prevention of infectious diseases available today. We consider it essential for all nursing homes to have a written protocol to verify and enhance the local vaccination programme; to this end, it is recommended that a record be kept of each resident's vaccination and that a protocol be established for action when a resident is detected who needs to update his/her vaccination schedule [10].

While we understand that it is not legally enforceable for workers or residents to provide vaccination information, a voluntary attempt to obtain such information on vaccination status is desirable and should be recorded in the medical records and medical information of the nursing home. Vaccination of workers against influenza and COVID-19 should be promoted by the nursing homes management as a principle of solidarity, ethics and protection of vulnerable people.

For further information, we refer interested parties to a recently published document entitled *The situation of vaccines for the prevention of infections in adults*: *An opinion paper on the situation in Spain* [11].

It is advisable to have a protocol for the prevention of any type of skin and soft tissue injury with risk of infection. It should be pointed out that in this field not only infections caused by bacteria should be considered, but also those potentially caused by viruses (Herpes zoster); fungi (*Candida* spp.) and parasites (scabies). To this end, daily skin checks are appropriate in facilities with a high risk of infection and with more than 50% of residents with a calculated Barthel score ≤ 55 points and in residents at the end of life. In addition to observing the skin daily for warning signs of pressure ulcer (PU), residents with predisposing factors (altered mental status, incontinence, obesity, malnutrition, smoking, reduced mobility, dehydration, etc.) should be identified early. And, of course, we should stress the importance of prevention of pressure injuries and also of moisture-associated skin damage, as well as monitoring for signs of infection in injuries that have already occurred.

The Norton scale (Table 2), which measures a patient's risk of pressure ulcers (PU), is also added.

Some recommendations for skin care include:

Keep the skin clean and dry, thus limiting the skin's exposure to moisture, urine and faeces. Use moisture barrier creams to protect the skin from urine and faeces. Change bed linen and clothing as often as necessary. Pay attention to buttons on clothing and wrinkles in sheets that may irritate the skin and frequent nappy changing (at least twice a shift).

For more detail on skin care considerations, see the SEGG's

protocols for basic care of the elderly [12], or the website of the National Group for the Study and Advice on Pressure Ulcers and Chronic Wounds (GNEAUPP) where a specific library can be consulted at the following link: https://gneaupp.info/biblioteca-internacional-de-heridas/.

Recommendations for the prevention and control of gastrointestinal infection. Infections by viruses (norovirus, rotavirus, etc.) and bacteria *(Salmonella*, *Shigella*, *Campylobacter*) are common causes of diarrhoeal disorders in people living in nursing homes, although *C. difficile* infection is particularly prevalent in this population and is related to antibiotic use.

At this point it is particularly important to take into account antimicrobial stewardship (AMS) programmes for the appropriate management of antibiotics in this population [13] of which the incidence of *C. difficile* infection (CDI) would be an indirect marker of antibiotic use or abuse.

CDI is a cause of severe diarrhoea in the elderly. Prevention of *C. difficile* transmission and infection remains a serious and difficult challenge in infection prevention and patient safety. We consider the control of antibiotic consumption to be the most important measure for the prevention of CDI and therefore recommend that all centres should keep a register of residents on antibiotic treatment, review the appropriate duration of treatment and avoid the use of empirical antibiotic treatment as much as possible.

Once a case of diarrhoea has been detected, other measures should be put in place to prevent the spread of infection, either by direct or indirect contact with the patient or their environment, and it is therefore recommended that residents be placed in contact isolation (single room; use of disposable gloves; hand hygiene with soap and water to wash away *C. difficile* spores as these are resistant to alcohols; use of disposable gowns if contact with the patient or their belongings is anticipated). In some care settings, where private rooms may not be available, other actions may be considered, including the use of spatial separation (a minimum distance of 1 metre between beds is recommended) to reduce the possibility of sharing items between the 'isolated' patient and others.

In addition, it is very important to reduce contamination of the resident's room by intensifying cleaning and disinfection measures, especially of objects or surfaces that are touched by hand, with chlorinated products for sanitary use.

Written protocols are needed to deal with potential outbreaks of HAIs. Outbreaks can be defined as unusual increases in diseases above baseline levels; surveillance and control of outbreaks should be a high priority. Issues to be considered in an outbreak management plan include: development of a case definition, case finding, outbreak analysis, formulation of a transmission hypothesis, design and evaluation of control measures, and reporting to Public Health.

The most common causes of outbreaks are respiratory and gastrointestinal infections. In some cases, a single case may be sufficient to trigger a response of the infection prevention and control programme. Examples of residential outbreaks include: influenza, tuberculosis, meningococcal meningitis, *Legionella* spp. infection, norovirus, salmonellosis, group A streptococcal soft tissue infection, viral hepatitis, scabies and infection with antibiotic resistant pathogens.

It is recommended that nursing homes that do not have their own pharmacy service establish an agreement with a community or hospital pharmacy in order to receive the necessary pharmaceutical coverage and care and to collaborate in epidemiological surveillance. The new regulation differentiates, as did RDL 16/2012, between homes with more and less than 100 beds for the purpose of establishing pharmaceutical provision. For nursing homes with more than 100 beds, a pharmacy service must be installed, while for homes with less than 100 beds, a variable system is established depending on whether the nursing homes are public or private.

The development of written recommendations for the prevention of transmission of eye infections and conjunctivitis is recommended. Outbreaks of ocular infection in nursing homes by both bacterial and viral pathogens are well described [14].

Prevention is therefore important to ensure the eye and general health of residents and should basically include measures such as hand hygiene of residents, visitors and caregivers and eyelid washing with clean, warm water or the use of special eyelid cleansing wipes [15,16].

Infection prevention and oral health issues. Oral health and hygiene are essential in reducing infections such as aspiration pneumonia [17] but it has also been shown that oral health can significantly affect overall health and is clearly related to the quality of life of older people. Therefore, we believe that oral health programmes should be promoted in nursing homes [18] providing information related to dental care and its importance both to the elderly and to their carers and relatives in order to detect oral diseases and treat them appropriately [19]. All this establishes the need for a close relationship between nursing homes and dental professionals [20-24].

DATA COLLECTION

Surveillance is important to detect outbreaks, changes in infection rates and other issues requiring infection control intervention (including the need for additional training or education of staff). The components of a monitoring system include a mechanism for data collection, a timetable and procedure for data evaluation, dissemination of results, and mechanisms for action and follow-up. Monitoring disease patterns over time can provide information on the effectiveness of changes in infection control practices and policies. An example of an institution data collection sheet, is provided in the Supplementary material-Annex 3.

Surveillance data can be collected through regular review of medical records, laboratory reports and other records. Monitoring compliance with infection control measures (process indicators such as hand hygiene compliance, catheter care and

Table 3 List of recommendations for the collection of data from institutions

Parameter	Institution	Description
Hospital admissions	All of them*	Hospital days/total days
CI of bladder catheterisation	High and medium risk	# of residents with catheter/total # of residents
CI of skin and soft tissue infection (SSTI)	High and medium risk	# of residents with SSTI/ total # of residents
CI of antibiotic treatment (ATB)	All of them*	# residents with ATB/total # of residents
CI of diarrhoea	All of them*	# residents with diarrhoea /total # of residents
Respiratory infection (RI)	All of them*	RI referred to hospital/total RI

*High risk: monthly; Medium risk: quarterly; Low risk: six-monthly; CI: cumulative incidence. #: number of

vaccination rates of staff and residents) is also an important component of infection prevention and control.

The frequency of data review will depend on the size and nature of the centre. Facilities at higher risk (High Risk) of HAI may need to review data at least monthly, while facilities at lower risk could be reviewed on a quarterly (Intermediate Risk) or six-monthly (Low Risk) basis.

Information on trends should be provided to units and employees, and be accompanied by action plans and follow-up.

This data set we advocate can result in an individual's data programme and an institution's data programme. The following are recommendations of its key features. An example of an electronic data sheet is provided in Supplementary material-Annex 4.

Individual monitoring programme: data collection at different points in time

On admission

We consider it necessary to have an individual file for each resident, which includes a complete geriatric assessment on admission, pharmacological treatments, and a social and medical assessment that allows for a complete final assessment of each resident.

Therefore, at the time of admission to a care home, in addition to the Individual Care Plan (ICP) drawn up by the interdisciplinary team of the centre, we believe it is necessary to have the following information in the file:

Checking the current adult vaccination schedule.

Episodes of infection, hospital admission and antibiotic use should be recorded for each individual. For persons with infections that are managed in the nursing home, at least daily recordings should be made of the following:

- Temperature, blood pressure, heart rate and oxygen saturation.
- Presence of bladder catheter.
- Presence of venous catheter.
- Presence of pressure injuries or moisture-associated skin damage.
- Presence of diarrhoea (>3 bowel movements/24 hours).
- Use of antibiotics (1 or more).
- Type of infection.

A sample data collection sheet is tentatively provided in Supplementary material - Annex 2.

Data Collection in Special Situations

After Hospital Admission

There is no data in the literature to support the mandatory systematic search for colonisation by Multi-Resistant (MR) Microorganisms in institutions that care for the elderly. However, we believe it is advisable to record infections caused by MR microorganisms and to record the carrier status of all residents returning from a hospital admission of more than 24 hours (Supplementary material - Annex 1: Resident Transfer Sheet); this pertains to the following microorganisms: Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, Carbapenemase-producing Enterobacteriaceae, MR *Pseudomonas aeruginosa*, MR *Acinetobacter baumanii* and MR *Stenotrophomonas maltophilia*. Gram-positive microorganisms should include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and *C. difficile*, although the latter is not genuinely MR.

Institution's data collection programme

As mentioned above, the collection, examination and evaluation of these data allow the detection of HAI problems and the search for solutions, the effectiveness of which can be recorded.

We understand that this programme cannot be the same in all institutions, because of the inequality of size and resources. The following (Table 3) is a list of parameters and recommendations according to the risk of HAI in nursing homes, which should be available to staff at these facilities. We consider it necessary for every RM to have a telephone list with contacts of interest, accessible to all employees of the institution. An example is provided in Supplementary material-Annex 5

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- Spanish Society of Chemotherapy (SEQ)
- Spanish Society of Clinical, Family and Community Pharmacy (SEFAC)
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- Spanish Society of General and Family Doctors (SEMG)
- Spanish Society of Geriatrics and Gerontology (SEGG)
- Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC)
- Spanish Society of Internal Medicine (SEMI)
- Spanish Society of Preventive Medicine, Public Health and Hygiene (SEMPSPH)
- Spanish Society of Primary Care Physicians (SEMERGEN)

TRANSPARENCY DECLARATION

For transparency purposes, we would like to inform you that GSK has contributed to the funding of this publication. Its content reflects the authors' own opinions, criteria, conclusions and/or findings, which may not necessarily coincide with those of GSK. GSK always recommends that its products are used in accordance with the technical data sheet approved by the health authorities.

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Review

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Tuberculosis in Spain: An opinion paper

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ABSTRACT

This document is the result of the deliberations of the Committee on Emerging Pathogens and COVID-19 of the Illustrious Official College of Physicians of Madrid (ICOMEM) regarding the current situation of tuberculosis, particularly in Spain. We have reviewed aspects such as the evolution of its incidence, the populations currently most exposed and the health care circuits for the care of these patients in Spain. We have also discussed latent tuberculosis, the reality of extrapulmonary disease in the XXI century and the means available in daily practice for the diagnosis of both latent and active forms. The contribution of molecular biology, which has changed the perspective of this disease, was another topic of discussion. The paper tries to put into perspective both the classical drugs and their resistance figures and the availability and indications of the new ones. In addition, the reality of direct observation in the administration of antituberculosis drugs has been discussed. All this revolution is making it possible to shorten the treatment time for tuberculosis, a subject that has also been reviewed. If everything is done well, the risk of relapse of tuberculosis is small but it exists. On the other hand, many special situations have been discussed in this paper, such as tuberculosis in pediatric age and tuberculosis as a cause for concern in surgery and intensive care. The status of the BCG vaccine and its present indications as well as the future of new vaccines to achieve the old dream of eradicating this disease have been discussed. Finally, the ethical and medicolegal implications of this disease are not a minor issue and our situation in this regard has been reviewed.

Keywords: Tuberculosis, situation in Spain, diagnosis, extrapulmonary tuberculosis, latent tuberculosis, pediatric tuberculosis, incidence, populations at risk, medical-legal aspects, recurrence, vaccines, treatment, new drugs, bedaquiline, delamanid, Intensive Care Unit, microbiological diagnosis.

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Tuberculosis en España: Un documento de opinión

RESUMEN

El presente documento es el resultado de las deliberaciones del Comité sobre Patógenos Emergentes y COVID-19 del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) en relación a la situación actual de la tuberculosis, particularmente en España. Hemos revisado aspectos tales como la evolución de su incidencia, las poblaciones actualmente más expuestas y los circuitos sanitarios para la atención a estos pacientes en España. Se ha discutido también la tuberculosis latente, la realidad de la enfermedad extrapulmonar en el siglo XXI y los medios de que en la práctica diaria se dispone para el diagnóstico tanto de las formas latentes como de las activas. La aportación de la biología molecular que ha cambiado la perspectiva de esta enfermedad ha constituido otro de los temas de debate. El documento trata de poner en perspectiva tanto los fármacos clásicos y sus cifras de resistencia como la disponibilidad e indicaciones de los nuevos. Junto a esto, se ha discutido la realidad de la observación directa en la administración de fármacos antituberculosos. Toda esta revolución está posibilitando el acortamiento del tiempo de tratamiento de la tuberculosis tema que ha sido igualmente revisado. Si todo se hace bien, el riesgo de recaída de la tuberculosis es pequeño pero existente. Por otra parte, muchas situaciones especiales han merecido discusión en este documento como por ejemplo la tuberculosis en edad pediátrica y la tuberculosis como causa de preocupación en cirugía y cuidados intensivos. Se ha discutido tanto la situación de la vacuna BCG y sus indicaciones presentes, como el futuro de nuevas vacunas que permitan alcanzar el viejo sueño de erradicar esta enfermedad. Finalmente, las implicaciones éticas y medicolegales que esta enfermedad plantea no son un tema menor y se ha revisado nuestra situación en este particular.

Palabras clave: Tuberculosis, situación en España, diagnóstico, tuberculosis extrapulmonar, tuberculosis latente, tuberculosis pediátrica, incidencia, poblaciones de riesgo, aspectos médico-legales, recidiva, vacunas, tratamiento, nuevos fármacos, bedaquilina, delamanida, Unidad de Cuidados Intensivos, diagnóstico microbiológico.

INTRODUCTION

Tuberculosis has accompanied mankind for as long as we can remember and continues to do so at the present time. The population of the economically richest countries, and some medical professionals, consider it an extinct or semi-extinguished disease of which the most basic reality is often ignored. We are talking about a disease that the World Health Organization has repeatedly failed to predict its eradication date and in which pandemics such as HIV and the great migratory phenomena have changed many aspects**.** Science, on the other hand, has been very active in this field of knowledge, with giant steps forward in the field of diagnosis, treatment and prevention.

For these and other reasons, the COVID and Emerging Pathogens Committee of the Illustrious Official College of Physicians of Madrid (ICOMEM), has asked itself about the recent state of tuberculosis in Spain and in its deliberations a series of questions have arisen to which we have tried to seek answers. On this occasion we have also turned to experts on the subject, from outside the Committee, who have helped us extraordinarily in the preparation and orientation of this document.

We will now go on to discuss the questions chosen, which we hope will be of interest to both physicians and the general public, both inside and outside our country. Nothing could be further from us than the pretension of being exhaustive and even less so in a subject such as this. As on other occasions, where scientific evidence has not been available, we have supplemented it with aspects of opinion that we wanted to share with our readers.

WHAT IS THE CURRENT SITUATION OF TUBERCULOSIS IN SPAIN IN TERMS OF NUMBERS AND WHERE HAVE WE COME FROM IN RECENT YEARS?

Tuberculosis (TB) has been a notifiable disease since the beginning of the last century. In addition, there is a special surveillance protocol for this disease approved in 2013 [1] which allows us to have updated information about it. Surveillance is a basic tool to monitor the achievements of the TB Control and Prevention Plan, developed by the Interterritorial Council of the National Health System in 2019 [2].

Based on data updated to March 2023, from the National Epidemiological Surveillance Network [3], in 2021, 3,754 TB cases were reported in Spain, of which 151 were imported. Thus, among non-imported cases (n=3,603), the notification rate (NR) was 7.61 per 100,000 population. This represents a decrease of 2.18% compared to 2020 (3,686 cases and NR=7.78) and 28.07% compared to 2015 (4,913 cases and NR=10.59). Consequently, Spain is a country with a low incidence of this disease. In addition, the first two goals of the TB Control and Prevention Plan were met in 2020 [2]. The first was to reduce the overall rate by 15%-21% in 2020 compared to 2015; and a reduction of 26.5% was achieved. The second target was to reduce the average annual rate of pulmonary TB (70% of all TB cases) by 4% in the period 2015- 2020; and a 6% reduction was achieved.

However, to achieve the end of TB, the World Health Organization (WHO) has proposed a 90% reduction in NR by 2035 compared to 2015 [4]. To achieve this, our rate would have to be reduced by 9.5% per year, a reduction greater than that observed in the 2015-2020 period, which was only 6%, and considerably higher than the 2.2% reduction recorded in 2021 with respect to 2020; therefore, if this rate of decline were to be maintained, the WHO target would not be achieved among us. The autonomous communities and cities with the highest NR in 2021 were Ceuta, Galicia, Catalonia, Rioja and the Basque Country, while those with the lowest

NR were the Canary Islands, Castilla La Mancha, Extremadura, and Navarre. And in practically all of them TB NR has decreased from 2015 to 2021.

In 2021, TB NR was always higher in men than in women (rate ratio 1.7) and was similar from 25 to 84 years of age. Almost half of the TB cases affected persons not born in Spain, and their mean age was considerably younger than that of those born in our country. It is noteworthy that 155 cases were reported in children under 15 years of age (79 in children under 5 years of age and 76 in the group aged 5 to 14 years). These figures are the lowest in the 2015-2021 period in Spain and represent a 54% decrease compared to 2015.

Of the total TB cases reported in 2021, 76.7% (n= 2,764) had information on HIV testing, with 179 (6.5%) testing positive. In 2021, 155 deaths were reported and TB mortality was 0.45 per 100,000 population. Mortality was higher in males than in females (2.6 times higher) and has followed a downward trend in the period 2015-2021.

Unfortunately, it has not been possible to assess, due to lack of adequate information (e.g., resistances), whether the two goals of the TB Control and Prevention Plan on TB treatment have been achieved; the goals were to achieve a treatment success rate of 95% for drug-sensitive cases and 75% in cases with resistances.

IS THERE CURRENTLY A POPULATION AT PARTICULAR RISK OF TUBERCULOSIS IN SPAIN?

No particular risk factors have been identified for the development of TB in Spain. However, at a global level, the National Epidemiological Surveillance Network has collected some traditional factors that could be associated with an increased risk [5]. Sex and age maintained their secular trend of higher frequency in men (male/female ratio of 1.7) and higher frequency of pulmonary forms in those over 65 years of age. However, the median age was 47 years in 2021 [3]. It does not appear, therefore, that these demographic characteristics allow the identification of any group at higher risk of the disease. There are, however, other factors that can identify a higher risk population. Coming from countries with a high incidence and prevalence of tuberculosis is undoubtedly one of these factors [3,5]. The country with the highest number of cases in the Registry was Morocco, followed by Romania, Bolivia, Peru and Pakistan [5]. It should be noted that, among this foreign population, the age at diagnosis of tuberculosis is lower (mean 39 years) and that more than half of the cases had been residing in Spain for more than 10 years and only 13% had been in Spain for less than two years. The other risk factor that continues to be recorded is HIV coinfection. The number of persons with tuberculosis who are HIV-positive has been declining and now accounts for 4.4% of the total (7% of those reported). This high frequency still makes it advisable to exclude HIV infection in persons with tuberculosis, regardless of age and presentation. Although persons with HIV present more frequently with extrapulmonary and systemic forms of tuberculosis, the majority remain pulmonary forms. Information on other risk factors (injection drug use, alcoholism, etc.) has recently been incorporated into the protocol of the National Epidemiological Surveillance Network, but data collection has still been scarce.

In summary, there is no population at particular risk of developing tuberculosis in Spain. However, coming from countries where prevalence is high and HIV infection identify two groups in which the suspicion of tuberculosis should be particularly high in the presence of a compatible clinical presentation.

IN WHICH CIRCUITS OF THE HEALTH SYSTEM ARE PATIENTS WITH TUBERCULOSIS DIAGNOSED AND TREATED IN SPAIN?

There are plans for the prevention and control of tuberculosis in Spain, both at the State and Autonomous Community levels [6]. These plans structure the strategic lines to be followed from the point of view of diagnosis and treatment, regardless of the level of care at which the patient is treated. The ultimate goal of these plans is to reduce diagnostic delay and treatment initiation, limit transmission and outbreaks, and prevent disease progression.

The symptoms of tuberculosis can be heterogeneous and non-specific, so it is very important to identify patients at risk (HIV, silicosis, poorly controlled diabetes mellitus, dialysis, transplant recipients, immunosuppressive treatment, nutritional deficiency and any condition that depresses the immune system) and socioeconomic circumstances that increase prevalence (malnutrition, poverty, overcrowding, drug addiction, migration from areas of high incidence).

Patients with suspected tuberculosis can present in any health care setting, whether primary or specialized care, so it is essential to carry out outreach sessions for health care professionals in order to make them aware of the problem that tuberculosis can pose.

The definitive diagnosis of tuberculosis is microbiological and will be carried out in laboratories with adequate facilities and will ensure that a complete diagnosis is made.

In the primary care setting, the microbiological studies necessary to establish the diagnosis can be requested, except for immunological tests, and treatment can be prescribed, although sometimes the patient is referred to specialized hospital care, mainly internal medicine, for evaluation of the situation. However, there is no protocol recommending referral to Hospital Specialized Care and it is more a personal criterion of the attending physician. On the other hand, Primary Care can carry out the contact study, focusing on the patients living with the case, and leaving the rest of the contact studies in the hands of Public Health. Patients with suspected tuberculosis are seen with some frequency in the emergency department [7], where the initial diagnostic tests may be requested and the patient may be referred to outpatient clinics or admitted depending on the patient's clinical situation.

WHAT DO WE UNDERSTAND BY LATENT TUBERCULOSIS, WHAT DOES IT REPRESENT IN SPAIN AND HOW SHOULD IT BE MANAGED?

Latent tuberculosis infection (LTBI) is defined by the presence of a state of persistent immunity to *Mycobacterium tuberculosis* in the absence of clinical manifestations of tuberculous disease. The WHO estimates that up to 30% of the world's population may develop LTBI in their lifetime, but obviously these figures vary according to the economic and social development of countries [8,9]. Thus, CDC publications estimate that 5% of the US population has LTBI. There is consensus that between 5 and 10% of people with LTBI will develop tuberculosis disease, with the risk of disease being higher in the first 5 years of primary infection and especially in children and immunocompromised individuals. There is also agreement that detection of LTBI in cases requiring treatment is essential for the prevention and control of the disease.

In countries with a low incidence of the disease (<100/100,000) and medium or high economic resources, a group in which Spain would be included, the WHO recommendations for the systematic diagnosis of LTBI and its treatment in case of confirmation, are established in two population groups [10]:

- High recommendation: patients with HIV infection, adults and children in contact with tuberculosis cases, patients who are going to start treatment with anti-TNF drugs, patients on dialysis, patients who are going to undergo bone marrow or solid organ transplantation and patients with silicosis.

Conditional referral to patients with socio-economic determinants: prisoners, healthcare workers, homeless, immigrants from high-incidence countries and drug users.

In Spain, the Strategic Plan for Tuberculosis Control, updated in 2019, adds other situations to be considered, such as aid workers and military personnel on mission in high-incidence countries, homes for the elderly, children who have traveled to high-incidence countries 10 weeks after their return, shelters for homeless people and people in immigrant care centers [11].

The strategic plan establishes among its indicators the proportion of subjects with a positive test and who are eligible for treatment and the percentage of subjects in which treatment is carried out. However, these indicators have only been reported by 5 autonomous communities and only in one of them were both percentages 100% [12].

The diagnosis of LTBI can be made by Tubercular Skin Test (TST) or interferon gamma release assays (IGRA). The comparative characteristics of the two tests are discussed elsewhere in this publication. A TST is considered positive when the induration of the papule exceeds 5 mm, although in subjects with a history of BCG vaccination the diagnosis of LTBI should be confirmed by an IGRA test [13,14].

A meta-analysis of data published up to December 2021 on the benefits and risks of screening patients with suspected LTBI has recently been conducted [9]. The paper included 113 publications but no studies directly evaluated the benefits and risks of screening. Pooled estimates of the sensitivity of the Tuberculin test (TST) were 0.80 at the 5 mm induration threshold, 0.81 at the 10 mm threshold, and 0.60 at the 15 mm induration threshold. The pooled estimates of the sensitivity of the IGRA tests ranged from 0.81 to 0.90. Overall, the pooled estimates of the specificity of the screening tests ranged from 0.95 to 0.99.

A randomized clinical trial (n = 27,830 subjects) found a relative risk of progression to active TB at 5 years after taking 24 weeks of Isoniazid (INH) of 0.35 compared to the untreated. Those treated with INH, however, had a higher risk of hepatotoxicity [9].

In LTBI prophylaxis, compared to INH monotherapy, adherence may be better with shorter combination treatments associating isoniazid with rifampicin or rifapentine. The guidelines established by the CDC in 2020 are as follows [15]:

Association of Isoniazid 300mg and Rifapentine 900 mg once a week under directly observed therapy for 3 months.

2.- Isoniazid 300mg/day plus Rifampicin 600 mg/day for 3 months.

3.- Isoniazid 300 mg/day for 6 months.

The consensus documents of the Spanish scientific societies also place the combination of rifampicin and Isoniazid in first place over Isoniazid alone [16,17] and the latest publications now include a regimen of isoniazid and rifapentine.

WHAT DO IGRAS PROVIDE AND HOW DO THEY COMPARE WITH TST IN THE DIAGNOSTIC CONTEXT?

The Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are diagnostic tests for *Mycobacterium tuberculosis* infection. Both rely on cellular immuno-response to mycobacterial antigens. The window period for detection ranges from 2-12 weeks, being shorter with IGRAs [18,19]. These tests cannot differentiate between a previous or current *M. tuberculosis* infection, nor between latent (LTBI) or active infection [20]. They are generally used as screening tests for LTBI in people who are at high risk of developing active tuberculosis.

The TST has been for many years the reference test used in the diagnosis of LTBI. It measures the delayed hypersensitivity reaction to a mixture of antigens common to different mycobacterial species contained in a purified protein extract (PPD). This multiple composition means that its sensitivity and specificity are not sufficiently high [18].

IGRAs were designed to complement the diagnosis of LTBI and detect the production of interferon gamma by T lymphocytes sensitized to *M. tuberculosis*, after stimulation with specific antigens [1,2]. The two main antigens used are the 6 kD *M. tuberculosis* early secretion antigenic target protein (ESAT-6) and the 10 kD culture-filtered protein (CFP-10), two strongly

Table 1 **Comparison between TST (Mantoux) and IGRAs for the detection of *Mycobacterium tuberculosis* infection.**

Features	TST	IGRAs
Antigens included in the test	Mixture of > 200 antigens of *M. tuberculosis* and other mycobacteria	2-3 types of antigens almost exclusive to *M. tuberculosis*.
Time to results	At least 48-72 hours	24 hours
Sample processing	No, in vitro performance	Yes, in vitro performance
Cross reaction	Yes, with BCG and MNT vaccination	Rare with BCG vaccination Only with some NTMs
Interference of results with recent viral infection and/or "live" virus vaccines[a]	Yes	Yes with vaccination Not clarified effects of acute infections
Window periods (mean)	2-4 weeks	8 weeks
Sensitivity	55-83%	52-94%
Booster effect[b]	Yes	No
Loss of sensibility in special populations	Yes	Yes Better performance than TST
Specificity	70-92%	90-100%
Cost	Low	Higher

NTM: nontuberculous mycobacteria; BCG: bacillus Calmette-Guérin.

[a]For example: measles, mumps, chickenpox, influenza.

[b]Positivization of previously negative TST due to tuberculin push effect in vaccinated patients or patients with decreased sensitivity to tuberculin.

immunogenic *M tuberculosis* antigens that are highly specific for *M. tuberculosis* [18,19]. However, they are not completely exclusive to *M. tuberculosis* and are also found in *M. africanun, M. bovis* (not in *M. bovis* - BCG vaccine) and in some non-tuberculous mycobacteria (*M. szulgai, M. flavescens, M. marinum* and *M. kansasii*), increasing the likelihood of false positives [18,19].

Among the main advantages of IGRAs over TST are the high specificity for the detection of *M. tuberculosis* in any type of population [20,21] and a higher sensitivity than TST [22]. They are especially useful in immunocompetent persons, older than 5 years of age [20,21,23]. Although the usefulness of this test is more limited in immunosuppressed patients, the specificity is higher than that of TST [24,25]. Despite their higher cost, IGRAs appear to be cost-effective in LTBI screening strategies in high-income settings for high-risk patients [26]. Newly developed or upgraded generations of IGRAs have shown similar diagnostic performance to older IGRAs and maintain the highest specificity relative to TST [27]. In addition, these new tests have demonstrated a good ability to rule out a diagnosis of active tuberculosis in clinical settings with a low to moderate prevalence of tuberculosis [28]. The advantages of IGRAs also include less likelihood of cross-reactivity to BCG vaccine and exposure to other non-tuberculous mycobacteria, less subjective interpretation, shorter window period, faster results, and the possibility of detecting false negative TST results due to skin anergy situations [18] (Tables 1 and 2).

For these reasons, IGRAs have now become the standard of care for detecting LTBI. In 2016 a Panel of experts from the Mycobacteria Study Group (GEIM) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Respiratory Diseases and Thoracic Surgery (SEPAR), developed an evidence-based guideline on the use of IGRAs to diagnose TB infection in immunocompetent and immunocompromised adults and children of any age with risk or suspicion of active TB [29].

WHAT IS THE STATUS OF EXTRAPULMONARY TUBERCULOSIS IN THE 21ST CENTURY?

Active tuberculosis outside the lung, the organ of entry and preferred target, is a frequent presentation within the large clinical spectrum of the disease. In classical series, extrapulmonary tuberculosis (EPTB) accounted for less than 20% of cases [30, 31]. In a small percentage (1 to 2%), the disease was disseminated, with a histological and clinical appearance of "millet grain" lesion seeding (Miliary Tuberculosis (MT), which evidenced the failure of the immune response and a fatal prognosis [32].

A number of causes have led to changes in the clinical presntation of TB, with a relative increase in EPTB [33-36]. These included the emergence of HIV as an emerging disease that greatly increased the risk of developing TB with a high proportion of EPTB [37-41]. Other forms of immunosuppres-

Table 2 Recommendations for the use of IGRAs in different clinical settings

Clinical environments	Recommendation	FR	Quality
IGRA for TB patient contact tracing	The panel suggests initiating contact tracing with the TST, but in BCG-vaccinated contacts, positive TST results should be confirmed with an IGRA performed on the date of TST reading.	Weak	Low to very low
IGRA for healthcare workers	Use TST for initial and periodic screening of health care workers, but positive TST results should be confirmed with an IGRA performed on the reading date. If TST becomes positive and IGRA remains negative, perform periodic screening with IGRA only if there is no suspicion of active disease or evidence of immunosuppression.	Weak	Moderate (IGRA) Very low (TST)
IGRAs for the diagnosis of active TB in children < 5 years old	In < 5 years with suspected active TB, the panel suggests using both TST and an IGRA to complement microbiological and radiographic studies for the diagnosis of active TB.	Weak	Very low
IGRA for contact tracing in children	In children > 5 years, initiate contact tracing with TST, but in BCG-vaccinated contacts, positive TST results should be confirmed with an IGRA performed on the date of TST reading.	Weak	Very low
	In children < 5 years, test with TST and IGRA, regardless of previous BCG vaccination.		
IGRA in HIV-infected persons	Use both TST and an IGRA to detect TB infection in persons with HIV infection. In persons with HIV and a CD4 cell count <200/mL, use only an IGRA.	Weak	Low to very low
IGRAs in patients with chronic inflammatory diseases (prior to initiating biologic therapies)	Use both PT and an IGRA to screen for TB infection in patients with chronic inflammatory disease before starting biologic therapy.	Weak	Low to very low
IGRA for patients requiring transplantation (SOT and allogeneic HSCT)	Use both TST and an IGRA to screen for TB infection in patients who will undergo solid organ or allogeneic hematopoietic stem cell transplantation.	Weak	Very low
IGRA for active TB	Do not use either IGRAs nor TST as a stand-alone test for the diagnosis of active TB.	Strong	Low
	The panel suggests using an IGRA as a test for TB infection to support the diagnosis in cases with a well-founded suspicion of active disease.	Weak	Very low

TST: tuberculin skin test; BCG: bacillus Calmette-Guerin; IGRA: interferon gamma release assays; HIV: human immunodeficiency virus; SOT: solid organ transplantation; HSCT: hematopoietic stem cell transplantation.
Modified from reference [29]

sion such as pharmacologically induced ones increase the prevalence of TB and the shift towards greater presence of EPTB or disseminated forms. Corticosteroids and treatment with Tumor Necrosis Factor alpha (TNF alpha) inhibitors [42] are two good examples of this. In these patients, EPTB accounts for 62% of all TB episodes [43,44].

Another group at risk for EPTB are solid organ transplant recipients (SOT) where EPTB may account for up to 25% of the episodes of tuberculosis infection and where therapeutic problems increase due to the risks of interference with the immunosuppressive drugs that these patients receive [45,46].

Immunosenescence in the elderly may also be a factor in the drift towards a higher percentage of EPTB forms [47].

Large series of patients with TB followed prospectively in our setting are uncommon and therefore, we provide here information from a hospital in Madrid (Ruiz-Galiana J and Barros C, personal communication) that illustrate the reality of TB and EPTB in our environment. In this center, 1,820 patients with active tuberculosis have been systematically collected over the last 40 years (1983-2023), with a median age of 37 years; 6.5% under 14 years of age and 16% over 65 years of age. Overall, 22.7% were immigrants (mostly Africans) and 17% of all patients in the series were HIV-positive [48]. In this experience, 45% were EPTB (22.8% isolated EPTB; 17.7% disseminated and 5% with two non-contiguous organs). Tuberculous adenitis remains the most frequent location of EPTB with microbiological certainty and in fact should be a permanent consideration in the differential diagnosis in the presence of lymph node enlargement [49,50].

Osteo-articular TB, especially infection of the axial skeleton (Pott's disease), is still relevant [51] as does monoarticular arthritis (hip and knee preferentially). Central Nervous System (CNS) TB continues to cause mortality and sequelae and in these forms the role of adjunctive corticosteroid therapy may decrease both the one and the other [52,53].

Intestinal tuberculosis, at least in developed countries, has decreased significantly both because of the decrease of highly bacilliferous forms and because of the sanitation of the cattle population *(M. bovis)* [48,54]. In the aforementioned series, the incidence of genitourinary TB also shows a decrease [55].

WHAT IS THE STATUS OF MICROBIOLOGICAL DIAGNOSIS OF TUBERCULOSIS IN SPAIN?

The diagnosis of tuberculosis in Spain, as in other high-income countries, has undergone a profound transformation with the introduction of new technologies and methods in laboratories and Microbiology Departments. However, at present, conventional methods such as smear microscopy, staining of respiratory and urine samples to visualize and quantify the presence of *M. tuberculosis*, and solid media cultures for isolation and phenotypic susceptibility studies coexist with new diagnostic methods. The latter include liquid cultures with continuous growth monitoring and the simultaneous possibility of studying susceptibility to drugs active against *M. tuberculosis*, molecular biology techniques, essentially nucleic acid amplification by real-time PCR, and IGRAs, the latter complementing the classic TST [56,57]. The introduction of new techniques has been aimed at improving diagnostic sensitivity and reducing laboratory response times.

In 2017, the Ministry of Health published a document containing the results of a survey reflecting the situation of tuberculosis diagnosis in Spain and updating previous data published in 2009. These data were to serve to boost the Network of Tuberculosis Laboratories at the national level [58]. In the survey published in 2017, 154 laboratories from 18 Autonomous Communities participated. It reflected that almost half of the laboratories did not perform cultures as they sent them to other centers or only performed microscopy techniques. Almost 40% performed microscopy and culture techniques, identification of the *M. tuberculosis* complex and antibiograms for first-line drugs, and 13% also performed antibiograms for second-line drugs. Interestingly, almost 45% of the laboratories had already adopted among their techniques one or more molecular systems capable of detecting the *M. tuberculosis* complex and simultaneously detecting resistance to rifampicin and/or isoniazid with the possibility of applying them either on direct samples or once *M. tuberculosis* had been isolated in the cultures. Likewise, 13% of the laboratories reported performing genotyping of multidrug-resistant strains, with this type of study being sent to a reference center in 70% of the laboratories. Confirmation of outbreaks was only performed in a few laboratories.

This situation would have changed today with the incorporation as standard in the diagnosis of tuberculosis of liquid cultures and rapid techniques based on real-time PCR that simultaneously detect the presence of the complex and rifampicin resistance. More recently, similar molecular systems have been incorporated that broaden the study of resistance markers to include isoniazid, fluoroquinolones and also amikacin, kanamycin, capreomycin and ethionamide [59]. Also, the incorporation of whole genome sequencing systems in many laboratories in the wake of the COVID-19 pandemic could be used in outbreak characterization.

The still existing deficiencies in TB diagnostic technology in the world constitute an unsustainable anachronism [60].

WHAT IS MOLECULAR BIOLOGY CONTRIBUTING TO THE DIAGNOSIS AND MONITORING OF TUBERCULOSIS IN SPAIN?

The availability of rapid molecular assays for the identification of the *Mycobacterium tuberculosis* complex, and even for the characterization of resistance mutations against first- and second-line antituberculosis drugs, has optimized the diagnostic capacity of laboratories and the possibility of establishing appropriate treatments early. However, there has not been a parallel development in the incorporation of molecular approaches for the monitoring and control of transmission. The molecular characterization of transmission "clusters" has provided valuable information for the precise determination of population environments associated with active transmission, revealing contexts and transmission dynamics that lie outside the circles of exposure contemplated by conventional contact studies [61].

Despite the great advances made by molecular epidemiology, the great social complexity of our populations, as a result of the increase in the immigrant population, often associated with suboptimal living conditions after arrival in the receiving countries, has demanded the application of higher resolution techniques. The incorporation of whole genome sequencing has opened a new era of genomic epidemiology [62], which represents a further increase in the accuracy of defining TB transmission patterns.

New genomic strategies have allowed us to shed light on the complexity of TB transmission in populations with high migration rates. Thus, we have been able to understand that in addition to cases that can be accurately labelled as imported cases, which reactivate the disease in our country, we identify cases resulting from new exposures after arrival in our territory.

The high resolution provided by genomic analysis must be coupled to a new way of conducting epidemiological research. It is only in this way that the linkages pointed out by the identification of genomic clusters can reveal the transmission environments behind them. This new way of working involves reorienting the patient interview to contemplate the links suggested by the genomic study, for which the use of community health workers who facilitate access to detailed information on these migrant patients is essential. The application of these strategies in complex populations has made it possible to effectively manage transmission alarms and even to identify such unexpected realities as transmission throughout the migratory journey [63].

For this new genomic approach to provide epidemiologically relevant information, it is necessary to make a population-based analysis effort and to maintain systematic analysis over a prolonged period of time. Persistent outbreaks of great magnitude have been identified in populations in our country in which this approach was used [64]. This method helps to find strains responsible for a large percentage of the cases in a population as well as to understand with high resolution the

dynamics of transmission [65]. In addition, the globalization of the new epidemiological scenario requires the transnational expansion of molecular and genomic studies, integrating our data with those of circulating strains in the migrants' countries of origin and in other European countries that receive migrants of the same nationalities [66].

The new challenge is to ensure that genomic results are obtained more quickly, so that they can be offered early to those responsible for surveillance programs and to efficiently direct control resources towards the environments that are truly responsible for the generation of secondary cases. The emergence of alternative sequencing systems, faster and more flexible, and with a discrimination capacity equivalent to that of conventional sequencing systems [67] allows to maintain expectations of accessing a true approximation of genomic resolution at the time of diagnosis. Thus, with the same analytical effort, it would be possible to access not only the essential data for the characterization of whether a new case belongs to an active transmission chain or not, but also to extract complete information about resistance mutations [68] or determine whether the case corresponds to a species of the tuberculosis complex other than MTB. Recently, a major zoonosis caused by *Mycobacterium caprae* was indirectly revealed by the application of genomic sequencing for epidemiological purposes [69].

The systematic genomic analysis of SARS-CoV-2 performed during the pandemic in our country has led to the provision of equipment and training in genomic strategies. It would be unforgivable not to take advantage of these resources and experience to achieve a transformation in the way in which TB transmission is being monitored and to ensure a definitive leap in efficiency on our way to its control.

WHAT IS THE RESISTANCE TO ANTI-TUBERCULOSIS DRUGS IN EUROPE AND SPAIN?

The prognosis of TB patients was truly dismal until the advent of the so-called "chemotherapy era". About 50% of patients could die, half of them within the first 18 months of having the disease, and the other half within 5 years. Another 20-25% of patients remained chronically ill in the community, without being cured, but also without dying. And only about 25-30% of patients were cured, because the immune system never stopped fighting against this pathogen [70].

The so-called "TB chemotherapy era" can be considered to have started with the discovery of streptomycin (1943), followed by PAS (1944), isoniazid (1951), pyrazinamide (1952), ethambutol (1961), rifampicin (1963), etc. The discovery of these drugs was followed by the development of multiple randomized clinical trials involving them, either alone or in combination. All this occurred in the two decades from 1943 to 1963, years in which not only 11 drugs with different activity against *Mycobacterium tuberculosis* were discovered, but also the bases that should govern all TB treatment were laid [71-74].

However, following the development of the different anti-TB drugs, resistance of *M. tuberculosis* to each of them began to be described, all as a consequence of their misuse. *M. tuberculosis* once again showed its capacity to adapt to adverse environments, in this case developing resistance to the different drugs [74]. These resistances have become a major problem worldwide, making it difficult to control the disease. The most important are rifampicin-resistant TB (RR-TB), which is still the most effective drug for treating TB; and multidrug-resistant TB (MDR-TB, which refers to TB with resistance to isoniazid and rifampicin) [75]. When, in addition to RR-RR/MDR-TB, there is resistance to fluoroquinolones, it is called pre-XDR-TB (pre-extensively resistant TB). And XDR-TB (extensively resistant TB) which is pre-XDR TB, which also accumulates resistance to linezolid, bedaquiline, or both) [75]. The main problem of resistance is that in order to avoid its selection it is necessary to associate a minimum of 2-3 drugs in the treatment of TB, and currently there are only about 20, of which only eight can be considered highly effective [71,74].

Unfortunately, the misuse of anti-TB drugs in the 1970s to 1990s caused MDR/MDR-TB to reach epidemic proportions worldwide. And cases of what is now called pre-XDR-TB began to appear. And this epidemic situation has only increased over the years of the current century, influenced by multiple factors, starting with the aforementioned inadequate treatment regimens, poor adherence to such prolonged treatment, the transmission of resistant strains of *M. tuberculosis*, access to drugs, the quality of TB control programs, etc. [74]. In fact, of the estimated 10.6 million TB cases worldwide in 2021 (a figure 4.5% higher than in 2020), nearly half a million (450,000) were ill with MDR/XDR-TB. Of the 1.6 million people who died of TB in 2021, about 250,000 were also MDR/MDR-TB carriers [76]. Consequently, drug-resistant TB, especially MDR/MDR-TB, remains a serious global public health problem that has required significant investment in the development of new diagnostic methods and new drugs [74].

It is estimated that almost 50% of MDR/MDR-TB cases worldwide occur in China and India, and another 7% in Russia and former Soviet countries [76].

Globally, it has been estimated that the proportion of new cases of RR-TB/MDR-TB was 3.9% in 2015 and 3.6% in 2021. These percentages rose in patients previously treated for TB, being 20% in 2015 and 18% in 2021 [76].

The WHO estimated that in 2021 there could be around 210 cases of MDR/MDR-TB in Spain (ranges 70 to 340), implying a rate of 0.43 cases per 100,000 inhabitants (ranges 0.15 to 0.72) [76]. WHO also estimated that in that year about 4.4% of new TB cases were RR-TB/MDR-TB (ranges 2 to 8.2), rising to 20% (range 5.9 to 44%) in previously treated patients [76]. These figures are very similar to those estimated at the global level worldwide [76], although in Spain there seems to be a clear difference between the autochthonous population with low rates of MDR/MDR-TB and patients born outside our country, with clearly higher figures [77]. Unfortunately, there are hardly any publications addressing this issue

Table 3	Situations in which the administration of directly observed anti-tuberculosis drugs (DOT) is considered a priority.
Treatment failures	
Relapses	
Drug resistance	
Intermittent patterns	
Previous poor adherence	
Prior TB treatment or chemoprophylaxis	
Indigence	
Active or previous drug addiction (drugs, alcohol, ...)	
HIV infection	
Children and adolescents	
Mental disturbances, cognitive impairment, psychological disturbances	
Blindness, deafness and frailty	
Institutionalized patients	

in Spain, but the few that exist offer much lower data than those estimated by the WHO, estimating that MDR/MDR-TB would be around 1% of new TB cases [77,78,79], or around 40-60 cases per year.

Worldwide, isoniazid (hr-TB) has the highest rate of resistance, clearly related to its introduction into the world almost two decades ahead of rifampicin. Globally, it is estimated to be around 8-10%, with the Eastern European region reporting the highest rates of Hr-TB, reaching 33.5% in new cases and 61.4% in previously treated patients. [80]. Again, the limited data available for Spain suggest that this rate may be around 5% in new cases [76-79].

WHAT DO WE UNDERSTAND BY NEW ANTI-TUBERCULOSIS DRUGS AND WHAT DO THEY CONTRIBUTE TO TREATMENT? WHAT IS THEIR STATUS IN SPAIN?

As we have mentioned, the poor prognosis of TB changed radically in the two decades between 1943 and 1963, years in which 11 drugs with different activity against *M. tuberculosis* were discovered and proved to be very effective in different associations, with the capacity to cure almost all of these patients [71,72,74]. However, when a highly effective scheme was developed at the end of the 1960s, it was thought that this disease could be eliminated in the short term, and research into the development of drugs with activity against *M. tuberculosis* was discontinued. It took more than 40 years for bedaquiline to be investigated as a new specific drug against TB [81].

Among the more than 20 drugs that are currently available with activity against *M. tuberculosis* [74], the vast majority are still the classics that have been used for decades, of which there was only one very good (rifampicin) and one quite good (isoniazid), the others having moderate or very poor action in many of them [71,74,82]. But since there was a treatment regimen that worked very well in the field, there was no concern to develop new drugs. It was only when cases of TB with rifampicin resistance (RR-TB) and with resistance to rifampicin and isoniazid (MDR-TB) started to increase considerably and reached epidemic proportions that we started to talk about possible cases of incurable TB again [83]. This is what prompted countries with more resources to start researching new drugs for TB, and to test antibiotics that had been shown to be highly effective against other infections for this disease [74,76,84].

Thus, the category of so-called new anti-TB drugs includes those that have been specifically investigated for TB and those antibiotics that, although never investigated for TB, have been shown to be very effective against this disease. Of the former, of those specifically investigated for TB, bedaquiline, delamanid and pretomanid are already available on the market, the latter two having a very similar action as they are both nitroimidazole derivatives. All three have excellent bactericidal and sterilizing activity, as well as being very well tolerated and preventing the selection of resistance [71,74,85]. This makes them clearly better than several of the classic so-called first-line drugs, such as pyrazinamide and ethambutol, and although they are currently only recommended for the treatment of RR-TB/MDR-TB, in the very near future they will certainly be part of the initial treatment regimens for TB with anti-TB drug sensitivity. In addition, more than 15 drugs are currently being investigated for TB and are in clinical phases I, II, or III. This shows the interest that, fortunately, TB is once again attracting research interest in countries with more resources.

On the other hand, there are other drugs that, although investigated for other infections, have been shown to be highly effective for TB. Among them are the fluoroquinolones moxifloxacin and levofloxacin, linezolid and clofazimine. All of them also have excellent bactericidal (except clofazimine) and sterilizing activity, as well as being well tolerated and preventing the selection of resistance [71,74,85]. This also means that in the very near future they will be part of the initial treatment regimens for TB. Finally, we can also consider as new drugs those that belong to families of so-called first-line drugs, but with some additional characteristics that can make them more effective in specific circumstances. This is the case of the rifamycins, rifabutin and rifapentine, which are quite similar in their action to the other rifamycin, rifampicin, but with a lower enzymatic induction in the microsomal cytochrome P450 in the former and a longer half-life in the latter. This is why rifabutin can be a very valid option in cases where the enzymatic induction of rifampicin can be a problem for the treatment of other diseases in which its drugs are metabolized in this cytochrome, as can happen with some anti-retroviral drugs and many other drugs [86]. And the longer half-life of rifapentine means that it can be used in weekly preventive treatment schemes (12 weekly doses of isoniazid plus rifapentine) [87], o that, with daily administration, their concentrations can be progressively increased and thus increase their sterilizing action, making it possible to shorten preventive treatment schedules (1 month with isoniazid plus rifapentine) [87] and curative of TB [88].

Therefore, the discovery of the so-called new drugs for the treatment of TB has been a major breakthrough in the treatment of this disease, especially because almost all of them are more effective than most of the previous ones (except rifampicin) and all of them have a very good sterilizing activity, which means to be able to shorten the treatment of tuberculosis infection and TB with drug sensitivity and resistance [71,74,85].

Unfortunately, access to some of these new drugs in Spain is quite difficult, in addition to being extremely expensive, as is the case with bedaquiline, delamanid and pretomanid, drugs that should now be considered in the first line of treatment of MDR/MDR-TB [71,74,75,85]. But one must be insistent in obtaining them, as they improve the prognosis with respect to the drugs previously used in the treatment of these forms of the disease. It can also be somewhat complicated to obtain clofazimine, although much less so than the previous ones. Fortunately, in Spain there is no problem in obtaining the fluoroquinolones levofloxacin and moxifloxacin, nor linezolid. Finally, however, it is still impossible to obtain rifapentine, since the European and Spanish Medicines Agencies have not yet approved it for use in Europe and Spain [89]. It is desirable that this situation will change in the very short term since, as has been mentioned, this drug is now part of shortened TB preventive and curative treatment schemes.

WHAT IS THE REALITY OF DIRECTLY OBSERVED (DOT) TREATMENT IN SPAIN?

Once the tuberculosis disease has been diagnosed and the appropriate treatment regimen has been selected, most patients should be cured, if they follow the treatment correctly. In high-income countries, most patients receive self-administered treatment. However, WHO data estimate that between 50-80% of patients on self-administered therapy do not take their treatment properly, especially 6-8 weeks after the start of treatment [90]. Poor adherence conditions the appearance of failures, relapses and/or selection of resistance. For decades, the WHO has been recommending supervised or directly observed therapy (DOT), which consists of seeing and ensuring that the patient takes the medication, ideally in the presence of healthcare personnel, rather than by members of the patient's entourage. With DOT, the probability of treatment completion increases to almost 90% [91]. DOT is also endorsed by other institutions including the American Thoracic Society (ATS), the Center for Disease Control (CDC) and the Infectious Diseases Society of America (IDSA) [3].

New technologies (SMS, cell phone alarms, video calls, etc) allow the use of systems that are less expensive than face-to-face DOT, but are not applicable to many patients. As of March 2023, CDC includes video (vDOT) as an alternative to face-to-face DOT [92].

In Spain, the implementation of DOT is very slow and is usually restricted to patients with a higher risk of poor adherence (Table 3). In addition to supervising the taking of pills, other actions such as: the provision of food, transport vouchers, psychological support, social workers, reminders or accompaniment for complementary tests and consultation check-ups, etc. help to achieve the objective. Although the ideal is to supervise daily intake at home, the DOT team could adapt, depending on the characteristics of the patients and the type of TB, to follow less strict guidelines (no weekends or holidays, allowing some short trips, etc.).

In Madrid, there is a DOT program that has been carried out by the Red Cross since 2002, which can be accessed by any hospital or primary care physician. Trained professionals (nurses and assistants) are distributed by health areas and go to the patient's home or to a previously agreed place to provide them with oral medication and even IM drugs (Streptomycin, Amikacin) if necessary. This structure and organization has been used for other medical needs such as detection of risk contacts, chemoprophylaxis in the family environment and even supervision of patients with problems unrelated to TB such as pregnant women with HIV infection requiring antiretroviral treatment, chronic hepatitis due to HCV or patients with atypical mycobacteria who, "a priori", are suspected to be poor compliers.

In the University Hospital of Móstoles over the last 20 years, the Red Cross DOT program has been used progressively (Barros C and Ruiz-Galiana J, unpublished data), reaching 409 episodes (65.4%) of the 625 diagnosed in this period of time with excellent results (only 3 failures, including 2 exitus). In recent years, more than 90% of the patients in this cohort, diagnosed with TB disease, joined the DOT program. The current question in such a situation is the selection of patients who do not require DOT and who can do the complete treatment on their own, without supervision. In some patients, where home treatment is not possible, DOT can be performed in long-stay centers (former "tuberculosis sanatoriums", old people's homes, psychiatric hospitals, prisons, etc..) or on an outpatient basis in drug dependency centers (DAC), soup kitchens or shelters.

HOW LONG AND HOW CAN THE DURATION OF ANTI-TB TREATMENT BE SHORTENED?

Difficulties in adherence to and completion of classic antituberculosis treatment led to the search for shorter duration regimens that would facilitate better compliance, allowing treatment to be completed more quickly. This search has been carried out both in patients with tuberculosis caused by microorganisms sensitive to anti-tuberculous drugs and in those caused by MDR or XDR mycobacteria.

Some of these regimens are outlined below:

Short regimens in drug sensitive tuberculosis

Regimen of choice: R (Rifampicin) I (Isoniazid) P (Pyrazinamide) E (Ethambutol) RIPE 2 months + IR 4 months

As opposed to the classic 9-month RIPE treatment, the current regimen of choice for tuberculosis in which resistance to first-line drugs is known or suspected to be absent is the

combination of RIPE, administered during an intensive phase of 2 months, followed by a consolidation phase of IR, administered for a further 4 months [93]. If it is confirmed that there is no resistance to isoniazid, ethambutol can be withdrawn from the intensive phase for the same duration. Only in case of cavitary disease and with persistent positive cultures at the end of the intensive phase is it recommended to extend the consolidation phase for an additional three months.

Alternative 1: RIPE 2 months + RI 2 months

Pulmonary tuberculosis can often be diagnosed in patients with compatible clinical and radiological findings in whom microbiological studies (stains, cultures) are negative. In these circumstances, in which it is assumed that the bacillary load should be low, the results of shortening conventional treatment have been investigated. Several studies have shown that reducing the time of RIPE administration from 6 to 4 months did not influence the rate of tuberculosis relapse [94-96]. For this reason, the most recent guidelines recommend that, after the initial phase of treatment with RIPE, the consolidation phase with isoniazid and rifampicin can be shortened to only two months [93]. This short regimen could be administered to HIV-negative individuals with culture-negative pulmonary tuberculosis in whom the clinical and radiological evolution is favourable after the two-month intensive phase. Treatment should not be shortened if there are doubts about the adequacy of the microbiological evaluation or if the response in the initial two months has not been good.

Alternative 2: Rifapentine-moxifloxacin 4 months

The efficacy of a 4-month regimen including rifapentine and moxifloxacin was recently reported [97]. This regimen for sensitive tuberculosis consists of an 8-week intensive phase of daily treatment with rifapentine, isoniazid, pyrazinamide, and moxifloxacin, followed by a 9-week continuation phase of rifapentine, isoniazid, and moxifloxacin (total of 17 weeks). According to the CDC, this short regimen would be an option for persons with TB lung disease caused by bacteria in whom drug resistance is not suspected, who are older than 12 years and weigh more than 40 kg, have a negative sputum culture (low mycobacterial load), and are not receiving medications that may interact with drugs in the regimen. In the case of persons with HIV, the CD4 count should be greater than 100 cells/microliter [98].

Short regimens in resistant tuberculosis

According to WHO and ATS/CDC/ERS/IDSA recommendations, patients with resistant tuberculosis should receive a long course of treatment with a total duration of 18-20 months or 15-17 months after culture conversion, with the possibility of modifying the duration depending on response [99]. In this long treatment, drugs are individualized and administered during an intensive phase extending 6 months after sputum culture conversion (performed two months after initiation of management). Subsequently, a continuation phase of 15-17 months from the time of sputum culture conversion is administered, continuing all drugs from the intensive phase except for bedaquiline, amikacin and streptomycin. In contrast to this long treatment, a short regimen that is standardized is proposed. Its efficacy was derived from a meta-analysis of observational studies [100] and was later confirmed in the STREAM study, a randomized clinical trial [101]. It starts with a 4-month intensive phase of moxifloxacin, kanamycin (or amikacin), prothionamide, clofazimine, high-dose isoniazid (15-20mg/kg/day), pyrazinamide and ethambutol which is extended to 6 months for smear positive and culture positive patients 2 months after initiation of treatment. Subsequently, a 5-month continuation phase of ethambutol, pyrazinamide, moxifloxacin and clofazimine is administered for a total of 9 to 11 months. The short regimen can be considered in patients who have not received previous treatment for more than 1 month with second-line drugs and in whom resistance to fluoroquinolones and injectable second-line drugs is excluded. Pregnant women, persons with extrapulmonary tuberculosis in coinfection with HIV or disseminated TB, meningeal or in the central nervous system are also excluded. In these circumstances, the long regimen should be administered. It should be noted that, although the short regimen has been recommended by the WHO, it has not been supported in the most recent recommendations of the ATS/CDC/ERS/IDSA, which consider that it has drawbacks, the evidence is inconclusive and call for the need to generate more evidence [93].

WHAT IS THE RISK OF RELAPSE FOR A PATIENT WITH WELL-TREATED TUBERCULOSIS?

According to WHO, recurrences of tuberculosis account for approximately 7% of incident cases [102]. A meta-analysis of [103] data from 145 countries suggests that the incidence of recurrent TB is 2.26 per 100 person-years, with a wide range between 0.05 and 29.52. This variability reflects the different definitions of recurrence and the settings in which it is analyzed, which include the comorbidities of the population, its socioeconomic level and bacteriological aspects, among others [104]. This is an issue of great importance in TB management programs, because recurrence is most often associated with resistance to treatment [102], and people with recurrent infection have a worse prognosis [102].

The most common cause of recurrence is lack of full adherence to treatment and it has been observed that administration under direct control can reduce recurrence rates by approximately 75%. However, the possibility of recurrence still exists [105].

Recurrences may be due to reactivation of the original strain (reactivations) or infection with a new strain (reinfections) [106]. The ratio of one to the other in recurrent episodes depends on several factors, including the adequacy of treatment and exposure to environments with high incidence of TB [103,107,108].

With respect to host characteristics, male sex, advanced age, low weight, smoking, diabetes or HIV infection are associated with a higher risk of recurrence [109-111]. From the social point of view, low income, low social or cultural level, immi-

grant status and prison stay are also factors associated with the risk of recurrence [107,109]. With respect to the first infection, the existence of cavitations and the persistence of *M tuberculosis* in the sputum two months after initiating treatment predict recurrence, most likely due to reactivation [107,109].

Most recurrences occur within the first two years of the first episode [110, 112], almost all of them (85%) in the first one [110], It therefore seems necessary to have a minimum follow-up period of one year after completing treatment, in order to diagnose them early. From the point of view of individual prevention, it seems necessary to insist on the need to correctly complete treatment, ensure the nutritional and health status of patients and help them to quit smoking. It is possible that pharmacological secondary prevention of TB may be useful in HIV patients [113], although prospective randomized studies are not available.

WHAT PROBLEMS DOES TUBERCULOSIS POSE AT PRESENT IN THE SURGICAL WORLD?

At present, the role of surgery in the treatment of tuberculosis has been relegated to treat its complications in those with poor clinical response or intolerance to medical treatment.

Surgery is considered when sputum cultures remain positive after four to six months of antituberculosis treatment and in the presence of complications (massive hemoptysis, persistent bronchopleural fistula, residual cavities, bronchial stenosis, pachypleuritis, tuberculous empyema) [114,115].

Surgery for tuberculosis is complex, due to the existence of numerous adhesions, pachypleuritis, pleural contamination and the presence of contaminated caverns in the parenchyma. Measures must be taken to avoid contamination of the contralateral lung, such as using a double-lumen tube for intubation. In general, surgery should be performed only after several months of antituberculous therapy, after negative cultures (if possible) [114,115].

Surgical techniques are diverse and are conditioned to the pulmonary functional reserve. These techniques cover a wide spectrum, from anatomical resections to temporary thoracostomies. In a meta-analysis [116] involving more than 6,000 patients, partial lung resection surgery was associated with greater treatment success (defined as no treatment failure and no relapse), but pneumonectomy was not. Treatment success was more likely when surgery was performed after culture conversion than before.

IS TUBERCULOSIS A CONCERN IN INTENSIVE CARE UNITS?

Approximately 3% of TB patients require admission to Intensive Care Units (ICU) with a high mortality rate (between 24 and 81%) depending on the social and geographical context [117].

The most frequent indication for admission to the ICU for TBI is acute respiratory failure due to pneumonia or acute respiratory distress syndrome (ARDS), which may or may not be accompanied by miliary tuberculosis, followed by septic shock with multiorgan dysfunction, adrenal insufficiency, tuberculous meningitis, and pericarditis. Other causes include thromboembolic disease, pulmonary haemorrhage, or pharmacological complications [118].

ARDS is the most frequent cause of admission to the ICU, although only 4% to 5% of ARDS are secondary to tuberculosis. Mortality in patients with ARDS reaches 60% in those requiring mechanical ventilation [119]. The nonspecific clinical and radiological findings require a high index of suspicion to reach a diagnosis. The management of ARDS is similar to that of other etiologies, being necessary to maximize protective ventilation measures, prone decubitus, sedation and deep relaxation. Recruitment manoeuvres should be performed with caution due to the high risk of pneumothorax.

Tuberculous meningitis is the second leading cause of admission to the ICU in tuberculosis patients, representing between 6% and 18% of all ICU admissions for TB. It is especially frequent in children, patients with miliary or disseminated TB and HIV coinfection. The most severe patients require neurocritical monitoring. Corticosteroids are used in conjunction with anti-TB drugs to reduce cerebral edema and reduce short-term mortality [120].

Despite adequate treatment, tuberculous meningitis has a high mortality (60%) and morbidity with residual neurological disability in 25% of cases.

Septic shock is generally associated with bacterial or other respiratory super-infection, with tuberculosis accounting for only 1% of the cases of septic shock in the ICU. It is very infrequent in immunocompetent patients and is associated with a very high mortality (80%) compared to other types of shock (48%). In patients with high clinical suspicion of TB, early initiation of empirical antituberculosis treatment is recommended, being the management of shock similar to that of other causes (fluid therapy and use of vasopressors). In refractory shock, adrenal insufficiency should be suspected and the administration of hydrocortisone (200-300 mg) should be considered [121].

Adrenal insufficiency is observed in 6 to 10% of patients with active TB due to direct involvement of the adrenal glands, hematogenous spread or the use of drugs such as rifampicin which increases cortisol metabolism and can cause functional adrenal insufficiency. In these cases the determination of plasma cortisol levels and the administration of hydrocortisone at doses of 300-400 mg /24 h or prednisone is recommended, avoiding dexamethasone because of its cushingoid side effects. Fludrocortisone should be added in patients with associated aldosterone deficiency.

The diagnosis and treatment of TB in critically ill patients poses several challenges, such as adequate specimen collection. Sputum or induced sputum is recommended in patients with noninvasive ventilation and endotracheal aspirate or bronchoalveolar lavage in patients with invasive mechanical ventilation. Appropriate samples should be taken from other locations according to the clinic such as pleural fluid, ascitic fluid and CSF or fine needle aspiration of peripheral lymph nodes.

In patients with high clinical suspicion, specific empirical treatment is essential. The characteristics of the critically ill patient, the route of administration, drug absorption, bioavailability, dose modification in case of hepatic and renal dysfunction, and interaction with other drugs should be considered to ensure adequate plasma levels. Conventional regimens (rifampicin, isoniazid, pyrazinamide and oral ethambutol) have been shown to reduce mortality compared to alternative regimens (IV levofloxacin plus oral ethambutol plus IM streptomycin or IV amikacin, without rifampicin or isoniazid) [122]. Suboptimal concentrations of some drugs lead to recommend the intravenous use of specific treatments that are not always available in all countries. The presence of MDR-TB should be considered if the patient comes from high-risk regions, has been previously treated with first-line drugs or has failed to respond to standard treatment [123].

Some patients present a paradoxical reaction after initiation of antituberculosis drugs characterized by rapid clinical deterioration (worsening or appearance of new lesions, airway obstruction, splenic rupture or neurological deterioration) due to reconstitution of immunity leading to an immune response against the bacilli. Corticosteroids are the mainstay of treatment.

Factors associated with high mortality in critically ill patients have been associated with age, presence of multiorgan dysfunction syndrome, sepsis, need for mechanical ventilation, development of nosocomial pneumonia, cardiogenic shock, renal failure, elevated APACHE II, HIV infection, low albumin, and delayed or inadequate treatment, among others [124]

Finally, it is necessary to isolate these patients, ideally in negative pressure rooms, reduce the procedures that generate the formation of droplets and aerosols, use closed suction systems and filters (in the expiratory branch) in mechanically ventilated patients and the use of personal protection measures including FP2 and FP3 masks by professionals according to the procedures.

WHAT IS NEW IN THE DIAGNOSIS AND TREATMENT OF CHILDHOOD TUBERCULOSIS?

Pediatric TB remains a major global health problem, with 1,200,000 new cases and 216,570 deaths by 2021, accounting for 12% of the global burden of the disease [102]. The risk of progression from infection to disease is substantially higher in children than in adults: approximately 30%-40% of infants and 10%-20% of children with latent infection progress to disease within 2 years of primary infection [125].

Definitive diagnosis of TB in children is difficult to establish due to the lack of specific signs and symptoms, difficulties in obtaining sputum samples, and the paucibacillary nature of the disease in this age group. As a consequence, less than half of children with TB have microbiological confirmation, despite improvements in diagnostic tools in recent years.

The cornerstone of the diagnosis of TB in children continues to be the chest X-ray (CXR), in postero-anterior and lateral projection [126], despite its low specificity and poor inter-observer agreement [127]. Computed tomography (CT) is more sensitive than CXR, but its systematic performance is not indicated due to the emission of ionizing radiation and the need for sedation in younger children [128]. Indications are [129]:

1) asymptomatic children with known contact, positive TST/IGRA and inconclusive CXR (or normal in <2 years),

2) symptomatic children with known contact, positive TST/IGRA and normal CXR, 3) immunosuppressed children with known contact, normal CXR, regardless of TST and/or IGRA,

4) children with doubtful or pathological CXR with possible airway compression or other complications that require further definition of the affected structures [129].

It can be very useful for the evaluation of recently infected children with lesions not evident on chest X-ray, as in the study of school outbreaks [7]. Thoracic and mediastinal ultrasound are increasingly used at the bedside to visualize consolidations, cavitations and miliary nodules [130] whenever they are in contact with the pleura, as well as mediastinal and, with more difficulty, hilar lymphadenopathies [131].

The sensitivity of immunodiagnostic techniques for TB infection in children, such as the TST and IGRAs, is lower than in adults. Recent studies show that the performance of the latest generation of IGRAs, QFT-Plus, is no better than the previous generation, QTF-Gold, or the TST: neither of these tests has sufficient sensitivity as a rule-out test in children with suspected TB disease [132]. Individually, their sensitivity is around 70-80%, but in combination it exceeds 90 [133]. For this reason, the recent Spanish pediatric guidelines [129] recommend performing both techniques to screen for infection in high-risk patients (immunocompromised patients of any age and under 2 years of age, extendable to 5 years in high-risk exposures), and performing only one, TST or IGRA, to screen for infection in low-risk patients (over 5 years of age, not immunocompromised). In patients with clinical suspicion of TB, both techniques are recommended in combination to maximize diagnostic possibilities (Tables 1 and 2).

As for microbiological diagnosis, smear microscopy and culture have suboptimal sensitivity in children (<15% and <50%, respectively) [134]. New molecular techniques such as GeneXpert have good sensitivity with respect to culture (66-81%) [135,136], offering rapid diagnosis in smear-negative children, they are recommended by the WHO for the diagnosis of pulmonary TB [126]. In recent years, several studies have demonstrated the usefulness of molecular diagnosis in stool samples, also endorsed by the WHO in the most recent guidelines, which is promising as it is a non-invasive sample [126,137]

Regarding new therapeutic developments [129], The doses of antituberculous drugs in children are shown in Table 4. The administration of treatment in this age group is particularly difficult since, with the exception of rifampicin syrup, they are not available in liquid formulations. Fixed-dose combination drugs ("FDCs") base their posology on the adult dose range, and are only authorized for use above a certain age and/or weight.

Table 4 Recommended doses of first-line antituberculosis drugs [129]

Drug	Dose in mg/kg/day (dosage range); maximum daily dose (in mg)	Comments
Isoniazid*	10 (7-15); 300	Risk of hepatotoxicity
Rifampicin	15 (10-20); 600	Poor CNS penetration; risk of hepatotoxicity
Pyrazinamide	35 (30-40); 2000	Risk of hepatotoxicity, skin toxicity or arthralgias
Ethambutol	20 (15-25); 2500	Poor CNS penetration; risk of optic neuritis

*** Pyridoxine (1-2 mg/kg/day; maximum 50 mg/day) should be supplemented if exclusive breastfeeding, vegetarian diet, malnutrition, patients with HIV infection and pregnant adolescents.**

A recent document provides practical recommendations for the administration of TB treatment in this age group [138].

Prophylaxis in contacts. Children under 5 years of age and immunosuppressed children in contact with a case of bacilliferous TB, once TB disease has been ruled out, should receive post-exposure prophylaxis with Isoniazid during the window period (8-12 weeks) until the immunodiagnostic study is repeated. Children older than 5 years who are not immunosuppressed do not require post-exposure prophylaxis during the window period.

Treatment of latent infection. Children with positive TST/IGRA, asymptomatic, and with normal imaging test, should receive treatment of latent infection. As a first choice, short regimens are recommended, such as H+R for 3 months [139], or R in monotherapy 4 months [140], better than the long regimens of H 6 months or H 9 months. Efficacy is similar in all regimens, with better compliance and lower toxicity in the short regimens.

Treatment of TB disease. In children with uncomplicated TB disease, the short 4-month regimen is recommended, based on the recently published SHINE trial [141], consisting of HRZ ± E for 2 months, followed by H+R for 2 months, provided the following criteria are met:

- Age between 3 months and 16 years.
- Negative smear microscopy.
- Non-severe disease: peripheral adenitis; intrapulmonary adenitis without airway obstruction; non-cavitated lung disease, limited to one lung lobe without miliary pattern, with/without uncomplicated pleural effusion.
- Strain susceptible or presumably susceptible to first-line drugs (H, R, Z and E).

In all other cases, conventional 6-month treatment should be administered, consisting of HRZ ± E for 2 months, followed by H + R for 4 months.

Treatment should be prolonged in children with osteoarticular TB (9-12 months), disseminated and miliary TB (6-12 months) and TB meningitis (at least 12 months). In children with TB of the central nervous system, intensive treatment with HRZ and ethionamide (ethionamide 15-20 mg/kg/day, maximum 1000 mg/day; 250 mg tablets) for 6 months could be considered, due to the better bioavailability of ethionamide in CSF compared to ethambutol. This regimen, implemented in high-burden countries, is not recommended in HIV-infected children.

WHAT IS THE CURRENT STATUS OF TUBERCULOSIS VACCINES?

There is currently only one licensed vaccine against tuberculosis, BCG (Bacille Calmette-Guérin). BCG, with more than a century of use and with variable protection against respiratory transmissible forms of the disease, is historically the most widely administered vaccine worldwide. It is estimated that about 4 billion doses of BCG have been administered, mainly in the context of routine immunization of newborns.

BCG is administered intradermally and at birth and its vaccination is recommended by the WHO and is included in the vaccination schedule of countries with a high incidence of tuberculosis. It is estimated that BCG vaccination coverage is close to 90% worldwide [142,143]. Based on WHO recommendations, BCG vaccination is not indicated in countries with a low incidence rate of the disease, defined as less than 10 cases of TB per 100,000 population per year.

BCG is a live attenuated vaccine derived from a strain of *M. bovis* belonging to the *Mycobacterium tuberculosis* complex that causes bovine tuberculosis. BCG was developed in 1921 by attenuation through successive passages of a strain isolated from a cow. This isolate was subsequently distributed to several laboratories around the world and after repeated subculture passages several different BCG vaccine strains were developed with multiple changes in the genome [144]. The main reason for BCG attenuation is the loss of the differential region 1 (RD1). In this RD1 region is located the gene coding for the ESAT-6 protein, which when secreted is one of the major virulence factors of the *M. tuberculosis* complex. ESAT-6, together with two other proteins encoded in this RD1 deletion, CFP10 and PPE 68, are potent antigens that are conserved in clinical isolates of *M. tuberculosis* and their loss in BCG, in addition to causing its attenuation, may be one of the causes of the lack of protection of BCG against pulmonary tuberculosis. The ESAT-6 and CFP-10 antigens are used in Interferon Gamma Release Assays (IGRAs) to differentiate BCG vaccination from *M. tuberculosis* infection.

In 1921, the first baby whose mother had died of TB after birth was vaccinated with BCG orally. In the following 6 years, more than 50,000 infants were vaccinated, demonstrating that the live attenuated BCG vaccine was safe and could protect against other infectious diseases. This "non-specific" effect of live attenuated vaccines would be at the origin of the significant decrease in all-cause mortality in "vaccinated" (less than 2 %) compared to mortality in "unvaccinated" (25 %). BCG, like other live attenuated vaccines, confers non-specific indirect beneficial effects through generalized stimulation of the immune system, which can protect against other pathogens. Since the 1960s, BCG has demonstrated its value as an immunomodulator, specifically in the chemotherapy of bladder cancers. The non-specific effects of BCG and other live attenuated vaccines were described by Peter Aabey and this mechanism of action is currently being studied in depth by Mihai Netea's team [145]. BCG administration at birth is able to induce a strong Th1-type immune response and has been shown to decrease the number of hospitalizations due to respiratory infections and sepsis [146].

BCG offers protection with 60-80% efficacy against meningeal and miliary TB, disseminated forms of tuberculosis that are accompanied by high mortality and occur mainly in childhood [147]. However, protection against pulmonary TB, the transmissible form of the disease, is variable, especially in adolescents and adults [144].

Since the 1990s, the association of HIV/AIDS and TB and the emergence of resistant strains have made it a priority to develop a new vaccine to protect against respiratory forms. As of 2023, 16 new vaccines are in various stages of clinical development, with the aim of protecting against respiratory forms of the disease and reducing its transmission.

Five of these vaccine candidates, or vaccine strategies, are in Phase 3 to study their efficacy. Among these candidates are the GamTBvac vaccine candidate, based on two protein subunits containing the ESAT-6 and CFP-10n antigens or the inactivated whole cell candidate MIP, based on *Mycobacterium indicus* pranii not belonging to the *M. tuberculosis* complex. Three other approaches use live attenuated vaccines among them the revaccination strategy with current BCG in adolescents and adults previously vaccinated with BCG at birth, secondly the vaccine candidate VPM1002, based on the use of recombinant BCG encoding for *Listeria* hemolysin and efficacy studies look for non-inferiority to current BCG and thirdly MTBVAC, the only candidate based on a live attenuated strain of a human isolate of *M. tuberculosis*. With respect to MTBVAC the main advantage over the other candidates is that it contains a larger repertoire of *M. tuberculosis* antigens. MTBVAC contains the genes encoding the immunodominant antigens absent in BCG, without causing virulence and safely provides more specific and durable immune responses in humans than BCG. Ongoing double-blind efficacy studies of MTBVAC are looking for greater protection than BCG against TB, with MTBVAC being a promising candidate [148].

If Phase 3 efficacy studies of any of these candidates show protection against TB disease superior to that obtained with BCG, a new generation of TB vaccines could be licensed in the next few years. Improved diagnosis, shorter duration treatment of TB, and the potential availability of a new vaccine effective against respiratory forms of the disease could make the dream of eradicating TB possible.

WHAT OBLIGATIONS AND LEGAL IMPLICATIONS ARE ASSOCIATED WITH THE CONFIRMATION OF A CASE OF ACTIVE TUBERCULOSIS IN SPAIN, AND WHAT ETHICAL ASPECTS SHOULD BE HIGHLIGHTED IN THIS REGARD?

Law 33/2011, General Law on Public Health in Spain, establishes the bases for the protection of health and the prevention of communicable diseases. According to this law, health authorities have the power to implement measures to control and prevent the spread of communicable diseases. If a person is diagnosed with TB, the health authorities must take measures to ensure that he/she receives appropriate treatment. These measures include notifying the competent authorities of the case, recommending or requesting treatment, monitoring compliance with treatment and, in exceptional situations, taking coercive measures to ensure treatment, such as compulsory hospitalization. When patients are offered TB treatment, they should usually be informed and their verbal consent should be sought [149]. It is important to emphasize that the goal is to show respect for the patient and thus increase the likelihood of treatment completion. Patients who refuse treatment or are noncompliant should be counselled about the risks to themselves and the community. Similarly, the physician should try to understand the reasons for the patient's refusal or noncompliance with treatment and attempt to select a method to overcome these difficulties. If the situation of refusal or noncompliance persists, the patient should be informed that, although he/she has the right to refuse care, if he/she has active tuberculosis and does not complete the required course of treatment, he/she may be placed in isolation or involuntary detention.

In this regard, several management options should be considered:

- Community management: In cases where patients are willing to receive treatment, isolation and detention are generally not necessary or appropriate. Home treatment of tuberculosis patients, with the adoption of appropriate infection control measures, does not generally expose other household members to any substantial risk. By the time a diagnosis is made, household contacts have already been exposed to the patient's infection, and the likelihood of contact infection decreases rapidly when treatment is initiated. Even in cases of patients who have MDR-TB or XDR-TB, community-based treatment models have been successfully implemented in a variety of settings [150-152].

- Isolation or detention should be limited to exceptional circumstances when the patient is:
  - contagious, and refuses treatment and all reasonable measures to achieve compliance have been attempted with unsuccessful outcome.
  - infectious and refuses to undergo evaluation, follow-up for infection.
  - contagious, has accepted outpatient treatment but does not have the capacity to establish adequate infection control.

It is necessary to clarify that in no case can treatment be imposed on patients who have TB despite their opposition. These patients should be given the opportunity to receive treatment, but if they do not accept it, their informed refusal should be respected, since, once isolated, the patient does not represent a risk to public health. Forcing these patients to receive treatment against their will is neither ethically nor legally admissible according to the principle and law of personal autonomy.

Isolation or detention should be considered exceptional, only when it is the only reasonable means of protecting the population. It should always follow the ethical and legal principles of:

- Be applied in accordance with the law based on a legitimate objective.
- Be the least intrusive and restrictive possible.
- Not be arbitrary, unreasonable, or discriminatory.

These principles are not legal obligations, they are a reflection of fundamental ethical values [149] such as the common good, patient participation and autonomy in decision making, effectiveness of the use of measures with plausible outcomes, and transparency and accountability in that measures are adopted in a manner open to all, with a fair, sensitive and evidence-based decision-making process.

In Spain, there is experience of actions by public health services to prevent the transmission of TB by non-compliant bacilliferous patients using the possibilities of Law 3/1986 (which is the Organic Law 3/1986, of April 14, 1986, on Special Measures in Public Health) [153]. They are based on the health authority's resolution of the need for localization and compulsory therapeutic hospitalization to administer the treatment, mobilizing police collaboration, communicating it to the affected person and requesting ratification by the Administrative Court. From July 2006 to June 2015, over 9 years, in this experience, such measures were only activated on 12 occasions. The authors conclude that such coercive legal measures should be used with prudence and proportionality, with the aim of allowing patients at high risk to be treated in their environment, thus reducing community transmission of infection [3].

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Application of CMO (capacity, motivation, and opportunity) methodology in pharmaceutical care to optimize the pharmacotherapy in older people living with HIV. DISPIMDINAC project

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ABSTRACT

Objective. To determine the effectiveness of a pharmaceutical intervention, based on the CMO methodology (capacity, motivation and opportunity), to decrease the prevalence of the PIMDINAC concept (potentially inappropriate medication+drug interactions+non-adherence to concomitant medication) in people living with HIV infection.

Material and methods. Longitudinal prospective multicenter study, conducted between October 2021 and October 2022. Patients living with HIV older than 65 years, on antiretroviral treatment and concomitant drug prescription were included. Demographic, clinical, and pharmacotherapeutic variables were collected. Pharmaceutical care was provided for 6 months according to the CMO model in each patient. The main variable was the percentage of patients who simultaneously fulfilled the PIMDINAC concept, comparing the baseline value with the same value at the end of the study. In addition, the percentage of patient's adherent to concomitant and antiretroviral treatment and the percentage of patients meeting the pharmacotherapeutic targets established for the prescribed medication at 24 weeks of follow-up were compared.

Results. Sixty-eight patients were included. Seventy-two percent were men, with a median age of 68 years. The median number of concomitant drugs was 7. A 60.6% of the patients had polypharmacy. The prevalence of the presence of the PIMDINAC concept decreased significantly (10.3 vs. 0%). In isolation, each of the aspects also decreased significantly (p<0.031). The percentage of patients who met the objectives improved significantly from 48,5 at baseline to 88.2 (p<0.001).

Conclusions. The pharmaceutical intervention based on the CMO methodology significantly decreased the prevalence of the PIMDINAC concept and increased the number of patients who achieved the objectives, optimising their pharmacotherapy.

Keywords: Pharmaceutical Care; HIV/AIDS; medication adherence; patient satisfaction; outcome assessment.

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Intervención farmacéutica basada en la metodología CMO para optimizar la farmacoterapia en pacientes VIH mayores. Proyecto DISPIMDINAC

Objetivo. Determinar la efectividad de una intervención farmacéutica, basada en la metodología CMO (Capacidad, Motivación y oportunidad) para disminuir la prevalencia de criterios PIMDINAC (medicación potencialmente inapropiada-interacciones farmacológica-no adherencia a la medicación concomitante) en pacientes VIH+.

Material y métodos**.** Estudio multicéntrico prospectivo longitudinal, realizado entre octubre-2021 y octubre-2022. Se incluyeron pacientes VIH+ ≥65 años, en tratamiento antirretroviral activo y medicación concomitante prescrita. Se recogieron variables demográficas, clínicas y farmacoterapéuticas. La intervención de atención farmacéutica se realizó durante los 6 meses de seguimiento a través de la metodología CMO. La variable principal fue la diferencia en el porcentaje de pacientes que presentaban los tres criterios PIMDINAC de forma simultánea al inicio-fin del estudio. Se analizó la variación del porcentaje de pacientes adherentes tanto al TAR y a la medicación concomitante, así como el porcentaje de pacientes que alcanzaron sus objetivos farmacoterapéuticos previamente definidos a los 6 meses de seguimiento.

Resultados. Se incluyeron 67 pacientes, 72.0% varones con una mediana de edad de 68 años. El 60.6% de los pacientes tenían polifarmacia de forma basal con una mediana de fármacos de 7.0. La presencia de criterios PIMDINAC disminuyó sig-

nificativamente de un 10.3 a 0%. De forma individual se redujo el porcentaje de cada criterio de forma significativa (p=0.031). Se incrementó el porcentaje de pacientes que alcanzaron sus objetivos farmacoterapéuticos (48,5% vs 88,2%; p<0.001).

Conclusiones. La estrategia basada en la metodología CMO disminuye significativamente la prevalencia de los criterios PIMDINAC, así como incrementa la consecución de los objetivos farmacoterapéuticos de los pacientes, optimizando su farmacoterapia.

Palabras clave: Atención farmacéutica; VIH/SIDA; adherencia a la medicación; satisfacción del paciente; evaluación de resultados.

INTRODUCTION

HIV infection is now considered a chronic disease due to the extraordinary decrease in mortality after the introduction of antiretroviral treatment (ART) and the subsequent arrival of new, more potent drugs with better dosages and with better dose regimens [1]. Increased survival has been accompanied by parallel ageing of people living with HIV (PLWH). In fact, as of 2030, more than 70% of HIV-infected patient cohorts in both the United States and Europe have a median age of more than 50 years, an aspect that will become more marked in the next decade [2].

At the same time, the older HIV population, considered older than 65 years of age, has also increased in the last decade [3].

The complexity of the approach to the PLWH is increasing. It is well known that aging in this population is more accelerated than in the non-HIV-infected population, which has brought with it the presence of a greater number of associated comorbidities and their necessary management, increasing the prescription of concomitant drugs reaching, according to the latest available data, the presence of polypharmacy is around 30-40% [4,5].

Some authors have highlighted the consequences of this polypharmacy, such as a greater number of interactions, even higher than in the general population, an increased presence of adverse effects and hospitalizations, and a high risk of falls and/or fractures [6,7].

The difficulty in the management of prescription associated with ART in this patient and the possible presence of potentially inappropriate drugs (PIM), is also higher than in the non-HIV population, particularly the prescription of anticholinergic drugs [8,9].

Some authors even mention that there may be an additional decrease in adherence to ART due to the presence of polypharmacy [8,9].

Guaraldi et al. [10] defined the so-called "iatrogenic triad" which includes, in older PLWHIV, the presence of polypharmacy, the prescription of medications that may be PIM for this population, and the possibility of relevant drug interactions (DI) between these drugs.

To carry out this qualitative and multidimensional management of polypharmacy in PLWH, PIMDINAC criteria have been developed. These criteria include interactions, potentially inappropriate drugs, and lack of adherence [11].

On the other hand, the new definition of pharmaceutical care (PC) [12] advocates a change of care orientation based on the direct relationship with the patient and the achievement and achievement of objectives in relation to pharmacotherapy, based on multidisciplinary and multidimensional work. This methodology of PC is called CMO, based on the three pillars that comprise it: capacity (stratification), motivation (objectives in relation to pharmacotherapy) and opportunity (new technologies) has already been developed and used in the PLWH, improving health outcomes, patient activation (knowledge, skills, beliefs, and confidence for managing health and health care), and patient experience [13-15].

The recent study carried out and published by Diaz-Acedo et al. [11] has shown that the prevalence of the PIMDINAC criteria [potentially inappropriate medication (PIM), drug interactions (DI) and non-adherence to concomitant medication (NAC)] is high in elderly PLWH, which requires a multidimensional approach to reduce their presence.

The aim of this study is to determine the usefulness of a pharmaceutical intervention based on the CMO methodology in reducing the prevalence of PIMDINAC criteria in PLWHIV who undergo pharmacotherapeutic follow-up in outpatient pharmacy clinics of participating hospitals.

MATERIAL AND METHODS

Study design and participants. PLWHIV were prospectively recruited between October 2021 and October 2022 in 4 centres across Spain. Patients were 65 years of age or more, clinically diagnosed with HIV infection, receiving ART, with concomitant medication prescribed for at least three months prior to inclusion in the study, attending PC visits in a participating hospital pharmaceutical department for ≥1 year before the beginning of the study, and eligible to sign the informed consent. Patients were excluded if they were unable to complete the study questionnaires or were included in clinical trials during the study period.

Interventions. Patients received routinely applied pharmacotherapeutic interventions in ambulatory care patients according to the CMO PC model [15,16]. It consists of an initial stratification of patients at three levels according to the risk stratified PC model in PLWHIV of the Spanish Society of Hospital Pharmacy [16]. These patients received a structured PC corresponding to the predetermined interventions for each level of care. During the face-to-face visit to the Hospital Pharmacy Service, a motivational interview was conducted for each patient. In each interview, pharmacotherapeutic objectives were established or reevaluated, in consensus with the rest of the medical team taking care of the patient at all times.

Lastly, all patients received permanent contact tools (web: www.farmaciavalmecpv.com, telephone, email, etc.) with study pharmacists to resolve any incident or doubt related to their treatment at any time during the study.

Outcomes. Baseline demographic data (age, gender), HIV infection control variables such as viral load (copies/ml) and CD4 count at the time of inclusion (cells/µL) as well as comorbidities and pharmacological therapy were recorded at the initial clinical evaluation. To describe multimorbidity patterns, we use the categorization proposed by Prados-Torres et al. [17] who classified these patterns according to the comorbidities (Cardiometabolic, geriatric-depressive, chronic obstructive pulmonary disease and thyroid-mechanic pattern).

PIMDINAC evaluation

The prevalence of PIMDINAC criteria was defined as the main variable and classified into 2 categories: total (joint presence of the PIM + DI + NAC criteria) or partial (isolated presence of some criteria).

The STOPP-START (2014) criteria were used to identify PIMs [18].

To identify DI between ART and concomitant medication, the University of Liverpool database was used and only potential contraindications and interactions were considered clinically relevant [19]. For the identification of DI between different non-antiretroviral drugs, the Lexicomp® tool was used, considering DI grade D (potential) or X (contraindications) [20].

Adherence to ART and concomitant medication were measured with the simplified medication adherence questionnaire (SMAQ) and the Morisky-Green questionnaire, respectively. In addition, pharmacy dispensing records were also consulted. In both cases, patients were considered adherent if they obtained a positive score using the appropriate measurement instrument.

The SMAQ is a questionnaire based on the Morisky-Green questionnaire and developed in our setting that consists of six items that assess forgetfulness, routine, adverse events, and missing doses [21]. Meanwhile, the Morisky-Green questionnaire consisted of four items that evaluate forgetfulness, routine, adverse events, and, in contrast to the SMAQ, assesses the impact of feeling better and does not evaluate missing doses; we used the Spanish validated version in Spanish [22].

Adherence rate was quantified as the proportion of days covered (PDC) during the six months prior to the study according to filled e-prescriptions. We estimated the total days of supplies from the first to the last refill during the 6-month observation period divided by the total days of the treatment interval, defined as the time elapsed from the date of the first refilled prescription until the end of the observation period. A PLWH was considered adherent if the PDC was> 95% and was >95% and not positive on SMAQ (where positive means that there was a positive response to any of the qualitative questions), no more than two doses were missed over the past week, or if they had fewer than two days of total non-medication during the last three months.

To evaluate the adherence to concomitant medications, we only considered disease-modifying medications (e.g., treatment for diabetes, cardiovascular disease, etc.) but not symptomatic treatments (e.g., analgesics, medications for gastroesophageal reflux, etc.). Adherence to concomitant medication was defined as a PDC >90% and also the Morisky-Green questionnaire score was four [23].

Polypharmacy

Polypharmacy was defined as the use of six or more different drugs, including ART; major polypharmacy was restricted to the use of 11 or more different drugs [23]. To describe the patterns of polypharmacy, we use the categorization proposed by Calderón-Larrañaga *et al.* [24] who classified those patterns according to the type of disease they were intended to treat (cardiometabolic, depression-anxiety and mechanic-obesity). After categorizing a drug according to the anatomical therapeutic chemical classification system up to the first three levels, a patient was classified into a specific pattern when he received at least three drugs included in the pattern.

Health outcomes

The consequences of the CMO pharmaceutical intervention on health outcomes such as dyslipidemia, hypertension, and diabetes were established by measuring the number of patients who achieved pharmacotherapeutic targets according to their clinical characteristics, including: levels of glycosylated hemoglobin, total cholesterol, triglycerides, low-density lipoproteins, and blood pressure before and after the introduction of the PC model. For the rest of the pathologies without analytical parameters, therapeutic success was confirmed from clinical records of medical histories made by the multidisciplinary team that monitors the patient and the lack of need for new treatments prescribed in the period between two follow-up visits.

Statistical analysis. Quantitative variables were expressed as means ± standard deviations, or medians and interquartile ranges when appropriate. Qualitative variables were presented as counts. Differences in variables collected before and after the intervention were assessed using t-student or Wilcoxon tests for related groups to compare quantitative variables. To analyze the changes in dichotomous variables, McNemar's test was applied.

Data analysis was performed using the R studio program (v 1.1.456). A *p*-value of 0.05 or less was considered statistically significant.

Ethics. The study was carried out according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki. The study protocol and any other information that required prior approval was reviewed and approved by the ethics committee of the research center *Comité de Ética de Investigación Sevilla Sur (1321-N-21).*

RESULTS

A total of 68 patients were enrolled (Figure 1). Finally, no patients were lost to follow-up. The baseline characteristics of the patients are summarized in Table 1. More than three-quarters of the patients were men (83.3%) with a mean age of

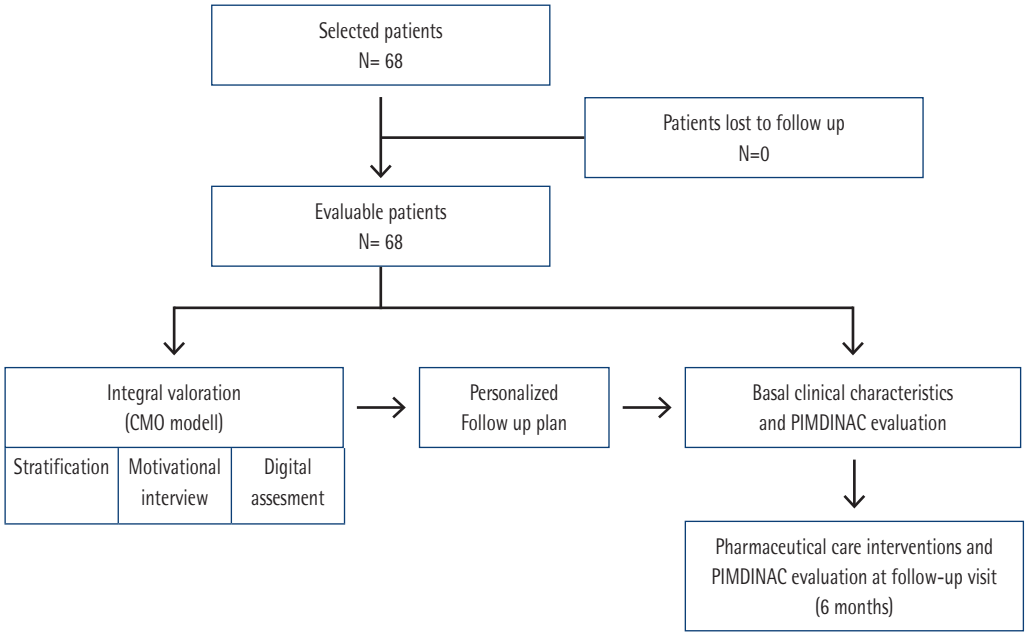

Figure 1 | **Study flow chart**

68±7 years. Most of them (59.0%) had sexually acquired HIV and responded well to the ART, with an undetectable viral load in 92.6% of patients and a CD4 count higher than 200 cells/uL in the 95.6% of them.

The most common ART regimens were those that included a combination of 'other combinations' (58.8), then two nucleoside reverse transcriptase inhibitors (NRTI) plus an integrase inhibitor (23.5%), followed by two NRTI plus a non-nucleoside reverse transcriptase inhibitor (10.4%) and, finally, two NRTI plus a protease inhibitor (2.9%). Among the treatments defined as other combinations, bitherapies such as DTG / 3TC or DRV/c+3TC and monotherapies such as DRV/c stand out.

Following indications from the CMO program, patients were stratified into three groups (Table 1). Six patients (8.8%) were at the high level, 38,2% at the intermediate level, and the remaining 36 patients (52.9%) were at level 3 (basal).

Based on these classifications and the conclusions of the motivational interview, specific pharmacist interventions were then applied to each patient. The interventions performed the most were for each pillar: Concomitant review and validation (91.2%), Review of objectives (82.4), Adherence (73.5%) and Safety (54.4%), and finally Fast Communication (32.4%) and Transversal follow-up (24.9%). Table 2 shows the interventions performed for each of the different patient visits according to the taxonomy of the methodology used.

Regarding the PIMDINAC criteria, a prevalence of 10.3% was found at the beginning of the study. At the end of follow-up, no patient met the concept globally (Table 3).

Regarding isolated criteria, significant differences ($p<0.005$) were found in the decrease in their prevalence at the end of follow-up.

Most of the patients were considered adherent to ART (92.6%). No differences were found at the end of follow-up.

Regarding concomitant medication, adherence was 55.9% at the beginning of the study. A total of 88.2% of patient's adherent to concomitant medication at follow-up at week 24 ($p<0.001$).

At baseline, 39 (57.4%) met the polypharmacy criteria and 10 (14.7%) had major polypharmacy. Among the patients evaluable for this outcome, the most frequent patterns of polypharmacy were cardiovascular and depression-anxiety (Table 1).

The mean number of drugs prescribed at baseline was 7.4 and decreased significantly at 24 weeks: 6.8 ($p<0.05$).

Significant differences were found in the percentage of patients who met the pharmacotherapeutic objectives planned by the health care team for each of the prescribed treatments at the end of follow-up: 48.5 vs 88.2 ($p< 0.001$).

DISCUSSION

Our multicenter study demonstrated that the PC CMO model, based on patient stratification, motivational interview, and the use of new technologies for the follow-up process, has a positive impact on health outcomes in PLWH, specifically with respect to drug optimization by reducing total and partial

Table 1 **Patient baseline characteristics.**

Characteristics	Total cohort (N= 68)
DEMOGRAPHIC	
Mean Age, years (SD)	68 (7)
Male gender, N (%)	57 (83.8)
HIV	
HIV acquisition, N (%)	
Sexual	36 (59.0)
Parenteral	25 (41.0)
Undetectable viral load, N (%)	63 (92.6)
CD4 count> 200 cells / u, N (%)	65 (95.6)
CD4 / CD8 ratio <1, N (%)	14 (20.5)
CLINICAL VARIABLES	
Coinfection HIV-HCV (n, %)	7 (10.3)
Geriatric-depressive comorbidities	17 (25.0)
Cardiometabolic comorbidities	53 (77.9)
Chronic Obstrucive Pulmonary Disease	7 (10.3)
Thyroid-mechanic	8 (11.8)
Charlson Index	5,5 (7)
PHARMACOTHERAPY	
ART (n, %)	
2 NRTI + 1 INI	16 (23.5)
2 NRTI + 1 NNRTI	10 (14.7)
2 NRTI + 1 boosted PI	2 (2.9)
Other combinations	40 (58.8)
STR	18 (26.5)
Polypharmacy	39 (57.4)
Major Polypharmacy	10 (14.7)
Patterns of polypharmacy	
Cardiometabolic	36 (53)
Psychogeriatric-anxiety	12 (17)
Mechanic-obesity	6 (8)
Cholinergic Burden	
High	3 (4.4)
Medium	3 (4.4)
Low	62 (91.6)
Stratification, n (%)	
Level 1 (>32)	6 (8.8)
Level 2 (18-32)	26 (38.2)
Level 3 (<18)	36 (52.9)

Table 2 Interventions carried out according to the CMO taxonomy of pharmaceutical care throughout the study.

	Basal n (%)	12 weeks n (%)	24 weeks n (%)
Capacity Interventions			
1.1 Antiretroviral treatment review and validation	50 (73.5)	45 (66.2)	46 (67.6)
1.2 Concomitant review and validation	68 (100.0)	63 (92.6)	62 (91.2)
1.3 Review of objectives	62 (91.2)	57 (83.8)	56 (82.4)
1.4 Coordination	43 (63.2)	30 (44.1)	19 (27.9)
1.5 Referral	12 (17.6)	3 (4.4)	4 (5.9)
1.6 Planning	59 (86.8)	51 (75.0)	44 (64.7)
1.7 Reconciliation	8 (11.8)	7 (10.3)	7 (10.3)
Motivational Interventions			
2.1 Safety	33 (48.5)	33 (48.5)	37 (54.4)
2.2 Special follow-up	25 (36.8)	19 (27.9)	15 (22.1)
2.3 Adherence	52 (76.5)	52 (76.5)	50 (73.5)
2.4 Motivation	35 (23.5)	35 (23.5)	18 (21.2)
2.5 Co-responsibility	25 (36.8)	23 (33.8)	20 (29.4)
2.6 Commitment	38 (55.9)	23 (33.8)	17 (25.0)
2.7 Information	38 (55.9)	27 (39.7)	29 (42.6)
2.8 Encouragement	24 (35.3)	11 (16.9)	8 (11.8)
Opportunity Interventions			
3.1 Fast Communication	31 (45.6)	20 (29.4)	22 (32.4)
3.2 Transversal follow-up	24 (35.3)	25 (36.8)	19 (27.9)
3.3 Transversal training	4 (5.9)	0 (0)	1 (1.5)
3.4 Social Coordination	1 (1.5)	1 (1.5)	3 (4.4)
3.5 Active Coordination	0 (0)	0 (0)	2 (2.9)

The taxonomy and description of the interventions are detailed in Morillo et al. [15].

Table 3 Prevalence of total and partial PIMDINAC criteria throughout the study.

Variable (n, %)	Pre-Post Analysis		Interaction p-value
	Baseline	Week 24	
PIMDINAC (total)	7 (10.3)	0	P=0.001
PIMDINAC (partial)			P<0.031
PIM	25 (36.8)	10 (14.7)	
DI	6 (8.8)	0	
NAC	27 (39.7)	7 (10.3)	
ART adherence	64 (92.6)	64 (92.6)	0.748
Adherence to concomitant treatment	38 (55.9)	60 (88.2)	0.005

ART: Antiretroviral treatment; DI: drug interactions; NAC: non-adherence to concomitant medication; PIM: potentially inappropriate medication.

prevention of the PIMDINAC criteria. Furthermore, we found that these personalized pharmacist-led interventions improved patient achievement of pharmacotherapeutic goals.

The life expectancy of PLWH has increased substantially. Consequently, older PLWH face many health challenges found in older healthy individuals, although the impact of ageing may be greater among PLWH. Previous studies have shown that personalized interventions led by pharmacists and based on the CMO model are well accepted by both patients and professionals, significantly improving health outcomes and reducing the risk of cardiovascular events [13,14]. In this study, the number of accepted interventions has not been specifically recorded, but given the high number and distribution of interventions carried out, it is reasonable to think that this line has been followed. Furthermore, the fact that the number of patients who reach their pharmacotherapeutic objectives is increasing by almost 40% reinforces this hypothesis and should also be the ultimate goal of this type of health interventions, according to the guidelines established by the different societies and entities around the world.

PIM were found in 36% of our elderly PLWH. This rate is lower than those reported in other studies [25,26]. This difference may be explained by the fact that our study could not include all the criteria that define inappropriate prescribing, for example: drugs prescribed without clinical indication; drugs administered beyond the recommended duration of treatment; drugs not adjusted to the patient's renal function or omission of prescription. Furthermore, the prevalence of drugs with an anticholinergic risk scale 3 was very low compared to the value of 17% reported by other authors [26] in PLWH, but in the line of HIV negative individuals in the same study. This could be explained by the number of drugs prescribed in our study (median 7), similar to the publication by Green et al. (median 6). Furthermore, differences in prescribing patterns between the United States and Europe could also explain this difference. However, it is a priority to develop a guide or tool of our own to establish what the real dimension of this problem is.

Our patients had a low percentage of treatments in the STR format. The use of complex associations of ARVs with comedications is expected to lead to an increased risk of DDI. Our results did not demonstrate a higher frequency of potential DDI in elderly PS compared to other published cohorts. This observation could be explained by the fact that HIV clinicians are aware of the potential for DDI of ART and therefore prescribe drugs without interaction potential, particularly in the elderly, improving the use of integrase inhibitors, with a better profile in this regard. Interestingly, the rate of potential red flag DDI was 8% at baseline and disappeared at the end of follow-up, which is very closely in line with the type of interventions most commonly performed during follow-up.

Another major concern in PLWHIV is the adherence to treatment, a variable negatively impacted by the therapeutic complexity resulting from HIV infection and comorbidities. Establishing PC in PLWH implies an increase in adherence and our results, which showed an increase in primary and secondary adherence, are in line with previous CMO-based PC, supporting the use of this model to improve patient adherence.

The prevalence of polypharmacy identified in our population is in line with studies published in our environment, which reinforces the idea that the characteristics of our population are similar to those of other cohorts from different hospitals [27,28].

Since the exponential growth of this problem is known for the coming years, this type of qualitative approaches should be implemented progressively and as a priority, according to the characteristics and resources of each center [29].

This study presents several strengths, including its prospective and multicenter nature. However, it also has some potential limitations. First, the lack of randomization with a limited sample size could be an important concern. However, we considered that there could exist participant bias when interventions resemble interventions in the putative control group, given the expansion and knowledge of the CMO PC model by many national hospital pharmacists and taking into account the results obtained in previous studies. For this reason, we considered that the best design to consider the influence of our pharmaceutical intervention was to use a pre-post design, so that each patient served as his or her own control. Furthermore, the study follow-up period can be considered relatively short within the life of a PLWH receiving chronic treatment. However, methodologically, it is robust enough to determine the impact of a structured health intervention. In this study, the 2017 stratification tool was used. In this sense, the distribution of patients by typology is within the percentages usually expressed (60-30-10 approximately). Although the tool has repeatedly reported advantages for PLWH, it is an instrument that is considered, at times, too complex. Therefore, a simplified adaptation was recently implemented [30]. This new tool has not yet been tested in the research setting, but given its simplicity, it should be easy to apply and reap greater benefits for practitioners, as it will allow further tailoring of interventions according to the multidimensional characteristics of patients.

Longer study periods will be necessary to determine whether the clinical effects observed after the CMO-based pharmacist intervention are preserved over time. Despite these limitations, this study has significant implications that highlight the importance of specialized PCs in the management of PLWH.

CONCLUSION

In conclusion, the PC CMO model, a pharmacist-led intervention based on stratification of patients according to their specific needs, in agreement with their pharmacotherapeutic objectives, and reinforced by motivational interviews and personalized follow-up using the new technological tools, could induce optimization of the pharmacotherapy of this type of patients and improvement of clinical outcomes frequently associated with HIV disease and improve, this way, their quality of life with the ultimate goal of successful ageing for older PLWH.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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Identifying the most important data for research in the field of infectious diseases: thinking on the basis of artificial intelligence

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ABSTRACT

Objectives. Clinical data on which artificial intelligence (AI) algorithms are trained and tested provide the basis to improve diagnosis or treatment of infectious diseases (ID). We aimed to identify important data for ID research to prioritise efforts being undertaken in AI programmes.

Material and methods. We searched for 1,000 articles from high-impact ID journals on PubMed, selecting 288 of the latest articles from 10 top journals. We classified them into structured or unstructured data. Variables were homogenised and grouped into the following categories: epidemiology, admission, demographics, comorbidities, clinical manifestations, laboratory, microbiology, other diagnoses, treatment, outcomes and other non-categorizable variables.

Results. 4,488 individual variables were collected, from the 288 articles. 3,670 (81.8%) variables were classified as structured data whilst 818 (18.2%) as unstructured data. From the structured data, 2,319 (63.2%) variables were classified as direct—retrievable from electronic health records—whilst 1,351 (36.8%) were indirect. The most frequent unstructured data were related to clinical manifestations and were repeated across articles. Data on demographics, comorbidities and microbiology constituted the most frequent group of variables.

Conclusions. This article identified that structured variables have comprised the most important data in research to generate knowledge in the field of ID. Extracting these data should be a priority when a medical centre intends to start an AI programme for ID. We also documented that the most important unstructured data in this field are those related to clinical manifestations. Such data could easily undergo some structuring with the use of semi-structured medical records focusing on a few symptoms.

Keywords: artificial intelligence, structured data, natural language processing, semi-structured medical reports.

Identificación de los datos más importantes para el desarrollo de inteligencia artificial en el campo de las enfermedades infecciosas

Objetivos. Los datos clínicos sobre los que se entrenan y prueban los algoritmos de inteligencia artificial (IA) proporcionan la base para mejorar el diagnóstico o el tratamiento de las enfermedades infecciosas (EI). Nuestro objetivo es identificar datos importantes para la investigación de las enfermedades infecciosas con el fin de priorizar los esfuerzos realizados en los programas de IA.

Material y métodos. Se buscaron 1.000 artículos de revistas de EI de alto impacto en PubMed, seleccionando 288 de los últimos artículos en 10 revistas de primer nivel. Los clasificamos en datos estructurados o no estructurados. Las variables se homogeneizaron y agruparon en las siguientes categorías: epidemiología, ingreso, demografía, comorbilidades, manifestaciones clínicas, laboratorio, microbiología, otros diagnósticos, tratamiento, desenlace y otras variables no categorizables.

Resultados. Se recogieron 4.488 variables individuales, procedentes de 288 artículos. 3670 (81,8%) variables se clasificaron como datos estructurados, mientras que 818 (18,2%) como datos no estructurados. De los datos estructurados, 2.319 (63,2%) variables se clasificaron como directas -recuperables a partir de historias clínicas electrónicas-, mientras que 1.351 (36,8%) fueron indirectas. Los datos no estructurados más frecuentes estaban relacionados con las manifestaciones clínicas y se repetían en todos los artículos. Los datos sobre demografía, comorbilidades y microbiología constituyeron el grupo más frecuente de variables.

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Conclusiones. Este artículo identificó que las variables estructuradas han constituido los datos más importantes en la investigación para generar conocimiento en el campo de la EI. La extracción de estos datos debería ser una prioridad cuando un centro médico pretende iniciar un programa de IA para la EI. También hemos documentado que los datos no estructurados más importantes en este campo son los relacionados con las manifestaciones clínicas. Estos datos podrían estructurarse fácilmente con el uso de historias clínicas semiestructuradas centradas en unos pocos síntomas.

Palabras clave: inteligencia artificial, datos estructurados, procesamiento del lenguaje natural, informes médicos semiestructurados.

INTRODUCTION

Artificial intelligence (AI) and personalised clinical care will be a forthcoming revolution in medicine [1–4]. The key to making this event possible is having high-quality data that can feed AI algorithms to achieve personalised diagnoses and help treat diseases. In the area of healthcare, an exponential amount of data is generated as each second passes and the potential for its use becomes greater [5]. However, there is little information on what data are integral to developing medical research. This point is of vital importance for several reasons: 1) to focus initial efforts on building AI programmes in Medicine with highly significant data; 2) to choose the best data extraction strategies for electronic health records (EHRs); and 3) to analyse the difficulties involved in assessing data quality. After analysing thousands of articles from the most important journals in our area of expertise—infectious diseases (ID)—our aim was to explore what kind of data are relevant for ID research to prioritise our retrieving EHR data model, establish the best systematic collection of such information, and determine the order of importance when developing semi-structured EHR systems.

MATERIAL AND METHODS

We perform a transversal and descriptive study to identify the most relevant data used in 10 different journals.

Screening. We screened 1,000 articles (a hundred of which were the latest in published articles across 10 different, high-impact journals specialised in either infectious diseases, tropical medicine, general medicine or multidisciplinary with articles published in the field of infectious diseases). High-impact journal was defined as a journal with the highest Journal Impact Factor. The Journal Impact Factor is a metric that quantifies the average number of citations received per article published in a specific journal within a designated period. The journals screened were The Lancet, The Lancet Infectious Diseases, The New England Journal of Medicine, Journal of the American Medical Association, Clinical Infectious Diseases, Clinical Microbiology and Infection, Emerging Infectious Diseases, The Journal of Infectious Diseases, PLOS Neglected Tropical Diseases and PLOS One.

We used the Web of Science Database with the next strategy search for each journal: SO= ("JOURNAL X") Refined by: RESEARCH AREAS: (INFECTIOUS DISEASES) AND DOCUMENT TYPES: (ARTICLE OR CLINICAL TRIAL) Timespan: 2018-2019. Databases: MEDLINE Search language=Auto. The search was conducted on 19/05/2019.

Inclusion criteria. Articles included for variable recollection had to fulfil the following inclusion criteria: 1) related to ID area in humans and 2) original studies with either clinical trials, observational/case-control design, or propensity score analysis, which presented clinical or epidemiological outcomes. A consensus team (AT, AL, FS, IG, CL and CGV) made decisions regarding the inclusion of certain articles when discrepancies arose. Exclusion criteria included non-related ID articles, animal studies, basic or microbiologic research, case reports, reviews, guidelines, letters or other types of non-original editorial research.

Variables and definitions. Variables from each article were introduced into a new database manually. Dichotomic, ordinal, discrete and continuous variables were considered as one variable, whilst nominal variables as one different variable for each instance. Variables were classified into either structured or unstructured data depending on whether the variable-in-question was retrievable in a structured table from our EHR. Additionally, when we could obtain data directly from our EHR, such structured data was classified as direct. In cases when an algorithm was needed, structured data was classified as indirect.

Lastly, variables were homogenised according to the nature of the variable. Therefore, homogenized variables were defined as variables that share the same data, but they are expressed differently in the articles. For example, here is a series of variables re-grouped within a category: age ≥65, age of children, age at delivery, age at diagnosis, etc, all of them were homogenized within the variable age. Finally, variable groups were rearranged according to the healthcare workflow within ID processes. The healthcare workflow was defined as the usual workflow used in the care of patients in the clinical field. It were defined by consensus eleven different healthcare workflow categories: epidemiology (e.g., incidence, prevalence, mortality, etc.), admission (e.g., admission unit, length of stay, etc.), demographics (e.g., age, sex, etc.), comorbidities, clinical manifestations, laboratory (e.g., blood test, serology, etc.), microbiology (e.g., isolated microorganism, antibiotic susceptibility, etc.) other diagnoses (e.g., pathology, images, electrocardiogram, etc.), treatment (e.g., antibiotics, antibiotic duration, etc.), outcomes (e.g., survival, cure rate, etc.) and other non-categorizable variables.

Statistical analysis. The qualitative variables were described as absolute and relative frequencies. The analysis was performed using SPSS version 24.0 software.

Ethics. No ethics approval was necessary due to the nature of our study.

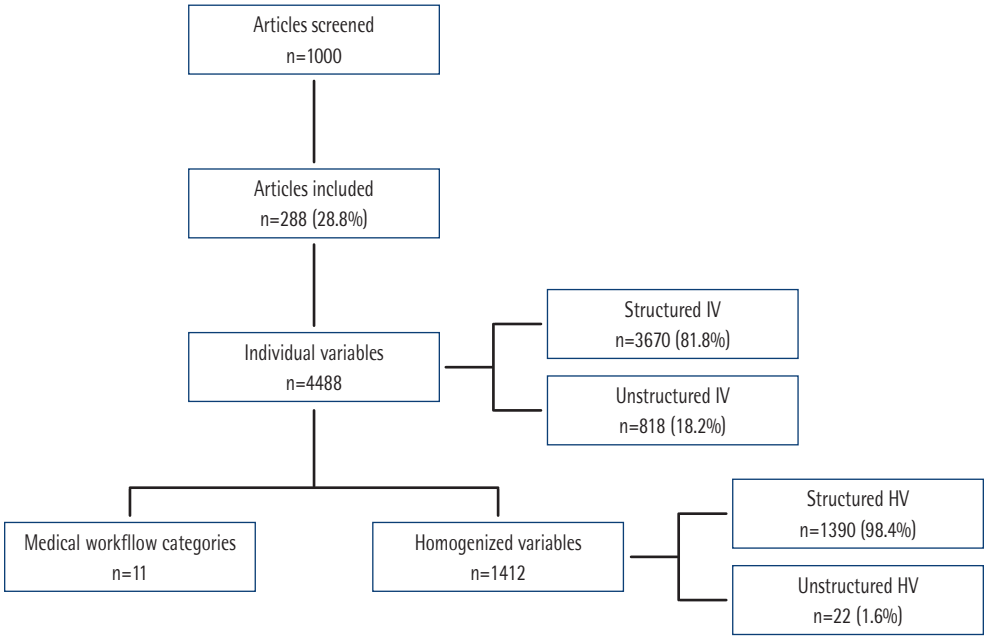

Figure 1 | **Workflow and processing of variables.**

Table 1 | **Articles included from each journal.**

Journal	n (%)
Clinical Infectious Diseases	38 (38)
Clinical Microbiology and Infection	26 (26)
Emerging Infectious Diseases	23 (23)
Journal of the American Medical Association	18 (18)
Journal of Infectious Diseases	41 (41)
The Lancet	25 (25)
The Lancet Infectious Diseases	38 (38)
The New England Journal of Medicine	42 (42)
PLOS Neglected Tropical Diseases	19 (19)
PLOS One	18 (18)

RESULTS

Screening. Of the 1,000 articles screened, 288 (28.8%) articles were selected for the study per criteria. From these articles, we collected 4,489 variables from our database (Figure 1) for final analysis. Table 1 shows those articles included, whilst Supplementary Table 1 provides specifications about each one included. From the 288 included articles, 110 (38%) were clinical trials, 149 (52%) observational studies, 14 (5%) case-control studies, 10 (3%) propensity score analysis and 5 (2%) other studies.

The most frequent data in the whole database. A total of 4,488 individual variables were collected from the 288 articles. Of these, 3,670 (81.8%) variables were classified as structured data and 818 (18.2%) as unstructured data. From the structured data, 2,319 (63.2%) variables were classified as direct, whilst the other 1,351 (36.8%) variables as indirect. Supplementary Table 2 describes all data collected, as well as homogenised variables (HV) and grouped variables per medical workflow details.

Homogenised variables. After homogenising the 4,488 variables, we obtained a total of 1,412 HV. When each of these HV were considered as one independent variable, 1,390 (98.4%) were structured data and 22 (1.6%) unstructured data. The twenty most frequent HV comprises 32.2% of all HV. Table 2 shows these twenty most frequent HV and their structured or unstructured data classification status.

Medical workflow categories. A rearrangement of the individual variables according to the medical workflow was conducted, and a total of 11 medical workflow categories (MWC) were created. These MWC were also classified into structured and unstructured data. From these MWC, demographics, comorbidity and microbiology were the most frequent variables. Table 3 shows the most common MWC and describes the frequency of each MWC as structured or unstructured data.

Table 2 The twenty most frequent homogenised grouped variables

Ranking	Grouped variable	Structured data in our EHR	Frequency n (%)
1	Clinical manifestations	No	325 (7.2)
2	Age	Yes	251 (5.6)
3	Gender	Yes	212 (4.7)
4	Race	No	90 (2.0)
5	Economic or work demographics	No	54 (1.2)
6	Other (non-homogenising variables)	No	47 (1.0)
7	Antimicrobial susceptibility	Yes	46 (1.0)
8	Body mass index	Yes	46 (1.0)
9	Housing characteristic demographics	No	45 (1.0)
10	Sexual behaviour demographics	No	44 (1.0)
11	Diabetes	Yes	40 (0.9)
12	Other comorbidities	Yes	37 (0.8)
13	CD4 count	Yes	36 (0.8)
14	Education demographics	No	28 (0.6)
15	Region	Yes	28 (0.6)
16	White blood cell count	Yes	28 (0.6)
17	Creatinine	Yes	26 (0.6)
18	Microorganisms	Yes	25 (0.6)
19	Country	Yes	24 (0.5)
20	Diagnosis	Yes	24 (0.5)

DISCUSSION

To our knowledge, this is the first study to detail which variables were the most important in the best recently published medical research to improve the management, diagnosis, treatment and/or outcomes of patients with ID.

These insights are essential when considering different objectives within the field of ID. Firstly, developing an AI programme is expensive and much of the cost may come from data collection [6]. Identifying which variables have contributed to generating the most current knowledge on the most important research topics in the field can help prioritise data extraction. It can also result in conceiving optimal strategies for retrieving such data from EHR.

Secondly, our study has identified that the most important variables in developing ID research are those that are structured. In fact, they represent more than 81% of the variables used in the articles reviewed. This information is of vital importance, because it facilitates the initial steps when creating and implementing AI programmes in hospitals. Obtaining structured data is less costly in terms of time and money than retrieving unstructured data. Moreover, finding objective criteria to check data quality is more feasible.

Lastly, our study provides new information on the most important unstructured variables used in advancing the field of ID. Currently, the only way to collect these variables is through natural language processing (NLP). NLP is complex and have significant shortcomings in medicine [7]. An objective analysis of this information arises due to the subjective perception of some clinical manifestations by patients; physicians' varying ways of writing clinical courses and discharge reports, including multiple acronyms and/or different languages; and the unpredictable and ambiguous nature of medical records. Therefore, the role of NLP has become extremely limited. However, our study has determined that many unstructured variables used in the ID research are related to clinical manifestations. This finding may help create a semi-structured clinical course for physicians.

Our study has some limitations. We performed the study in a single hospital, which has an EHR system based on SAP. Other hospitals with other EHR programmes may have structured data unavailable to us or, inversely, have data as unstructured that would otherwise be structured in our case.

Table 3 Frequency of medical workflow categories and classification status as structured and unstructured data.

Medical workflow categories Total variables = 4,488	Structured data in our EHR n (%)	Unstructured data in our EHR n (%)
Epidemiology	203 (4.5)	185 (4.1)
Admission	84 (1.9)	0
Demographics	664 (14.8)	251 (5.6)
Comorbidities	547 (12.2)	9 (0.2)
Clinical manifestations	195 (4.3)	325 (7.2)
Laboratory	317 (7.1)	0
Microbiology	513 (11.4)	13 (0.3)
Other diagnosis	477 (10.6)	11 (0.2)
Treatment	487 (10.9)	2 (0)
Outcomes	180 (4)	21 (0.5)
Other	1 (0)	3 (0.1)

Furthermore, our study focuses on what data are necessary to generate knowledge in the field of ID. Determining how to ensure that these high-quality data are retrievable should be the subject of future research.

To conclude, our study identified the most important variables that have been used in research to build knowledge in the field of ID. As methodologic approaches for obtaining unstructured data improves, healthcare programmes aimed at implementing AI in ID can work on extracting high-quality structured data. With these data, computer scientists and clinicians could strengthen a powerful base by which to develop potentially useful artificial intelligence algorithms in current medical practice. We also documented that the most significant unstructured data in ID are related to clinical manifestations and could be easily structured with the use of semi-structured medical records focusing on a few symptoms.

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CONFLICT OF INTERESTS

PP-A has received honoraria for talks on behalf of Merck Sharp and Dohme, Gilead, Lilly, ViiV Healthcare and Gilead Science. AS has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, Menarini, Angellini, as well as grant support from Pfizer. PC has received honoraria for talks on behalf of Gilead Science, MSD, Pfizer, Janssen and Alexion. CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, GSK, and Menarini, as well as a grant from Gilead Science, Pfizer and MSD.

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Evolución de los serotipos causantes de enfermedad neumocócica invasiva aislados durante 2008-2022 en un Hospital Público Madrileño de nivel dos, en relación con su inclusión en diferentes vacunas conjugadas

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RESUMEN

Introducción. El uso de vacunas conjugadas frente a *Streptococcus pneumoniae* ocasiona cambios en la epidemiología de la Enfermedad Neumocócica Invasiva (ENI). El objetivo de este estudio fue analizar la evolución de los serotipos de *S. pneumoniae* aislados en el Hospital Universitario de Getafe entre 2008 y 2022.

Material y métodos. Se estudiaron 313 cepas de *S. pneumoniae*. El serotipado se realizó mediante el test de aglutinación por látex (Pneumotest-latex) y la reacción de Quellung. Además, se determinó la concentración mínima inhibitoria (CMI) frente a penicilina, eritromicina y levofloxacino por el método de gradiente de concentración (E-test) según los criterios de corte EUCAST.

Resultados. Los serotipos más frecuentes en todo el periodo de estudio fueron 8, 3, 19A, 1, 11A y 22F correspondiendo con el 46,6 % de los aislados. Durante los años 2008-2012, los serotipos 3, 1, 19A, 7F, 6C y 11A supusieron en conjunto el 53,6% de los aislamientos. Entre 2013 y 2017 los serotipos 3, 8, 12F, 19A, 22F y 19F representaron el 51% de los aislados. Entre 2018-2022 los serotipos 8, 3, 11A, 15A, 4 y 6C incluyeron al 55,5% de los casos. En total, 5 cepas (1,6%) se mostraron resistentes a penicilina, 64 (20,4%) resistentes a eritromicina y 11 (3,5%) resistentes a levofloxacino. Los niveles de CMI_{50} y CMI_{90} frente a los tres antibióticos se mantuvieron estables a lo largo del tiempo.

Conclusiones. El uso de vacunas conjugadas condicionó un descenso de los serotipos cubiertos junto con un aumento de los no vacunales. Los patrones de sensibilidad a eritromicina y levofloxacino se mantuvieron relativamente estables. La resistencia a penicilina fue muy baja, no encontrándose este tipo de cepas resistentes en el último periodo de estudio.

Palabras clave: *Streptococcus pneumoniae*, serotipos, vacunas, sensibilidad antibiótica

Evolution of the serotypes causing invasive pneumococcal disease along 2008-2022 in a Level 2 Public Hospital of the Madrid Region, in relation to their inclusion in different conjugate vaccines

ABSTRACT

Introduction. The use of conjugate vaccines against *Streptococcus pneumoniae* originates changes in the invasive pneumococcal disease (IPD). The aim of this study was to investigate the evolution of *S. pneumoniae* serotypes isolated in the Hospital Universitario de Getafe between 2008 and 2022.

Material and Methods. 313 of *S. pneumoniae* strains were studied. Serotyping was carried out by latex agglutination (Pneumotest-latex) and the Quellung reaction. In addition, the minimal inhibitory concentration (MIC) was determined against penicillin, erythromycin and levofloxacin by the concentration gradient method (E-test) according the EUCAST breakpoints.

Results. The most frequent serotypes throughout the study period were 8, 3, 19A, 1, 11A and 22F corresponding to 46.6% of the isolates. Along 2008-2012 the serotypes 3, 1, 19A, 7F, 6C and 11A represented altogether 53.6% of the isolates. Between 2013 and 2017 the serotypes 3, 8, 12F, 19A, 22F and 19F grouped 51% of the isolates. During 2018-2022 the serotypes 8, 3, 11A, 15A, 4 and 6C included the 55.5% of the cases. In total 5 strains (1.6%) were penicillin resistant, 64 (20.4%) erythromycin resistant and 11 (3.5%) levofloxacin resistant. The MIC_{50} and MIC_{90} levels maintained stables along the time.

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Conclusion. The conjugate vaccines use with different serotype coverage conditioned a decrease of the vaccine-included and an increase of non-covered. Despite these changes, the global antimicrobial susceptibility patterns to erythromycin and levofloxacin maintained relatively stables. The resistance a penicillin was low, not finding this type of resistant strains in the last study period.

Keywords: *Streptococcus pneumoniae*, serotypes, vaccines, antimicrobial susceptibility

INTRODUCCIÓN

Streptococcus pneumoniae ocasiona un amplio espectro de infecciones. Las de mayor importancia son las incluidas en la denominada Enfermedad Neumocócica Invasiva (ENI) que viene definida por el aislamiento de la bacteria en muestras clínicas habitualmente estériles. La ENI, es una enfermedad de declaración obligatoria (EDO) en la Comunidad de Madrid desde el año 2007 [1]. Actualmente, la inmunización con vacunas conjugadas representa la mejor forma para su prevención. En el año 2006 fue incluida en la Comunidad de Madrid, la vacuna neumocócica conjugada 7-valente (VNC7) frente a los serotipos 4, 6B, 9V, 14, 18C, 19F y 23F, con una pauta de dosis tres más uno (2, 4, 6 y 18 meses de edad). Posteriormente, en años siguientes, se desarrollaron dos vacunas neumocócicas conjugadas para su uso en niños. La 10-valente (VNC10), que añade los serotipos 1, 5 y 7F y la 13-valente (VNC13), que cubre adicionalmente los serotipos 3, 6A y 19A. En la Comunidad de Madrid se empleó en el calendario de vacunación infantil la VNC7 hasta junio de 2010, cuando fue sustituida por la VNC13, con una pauta dos más uno (dosis a los 2, 4 y 15 meses de edad). No obstante, en julio de 2012, esta vacuna fue retirada del calendario de vacunación infantil permaneciendo únicamente en grupos de riesgo, aunque su administración no financiada, siguió siendo recomendada por los pediatras durante este tiempo con una pauta tres más uno (dosis a los 2, 4, 6 y 15 meses). Finalmente, en el año 2015, se aprobó un nuevo programa de vacunación infantil, incluyendo de nuevo, la VNC13 con una pauta dos más uno (dosis a los 2,4 y 12 meses) [1,2]. La VNC13 reemplazó en enero de 2018 a la vacuna neumocócica polisacarídica 23-valente (VNP23) para su uso en adultos con patología crónica de base y de alto riesgo con cualquier edad [3]. Existe otra nueva vacuna conjugada 15-valente (VNC15), que adicionalmente incluye los serotipos 22F y 33F y se ha mostrado tolerable, inmunógena y segura [4,5]. Esta vacuna ya ha sido también aprobada para su uso en niños [6].

La nueva vacuna 20-valente (VNC20), que añade a todos los serotipos de la VNC15 los serotipos 8, 10A, 11A, 12F y 15B también ha sido aprobada en 2022 para su uso en adultos de más de 18 años [7,8] y en abril de 2023, esta vacuna se introdujo en la Comunidad de Madrid en el esquema de vacunación frente a neumococo para la población adulta [9].

Recientemente se ha desarrollado otra nueva vacuna conjugada 21-valente para adultos (VNC21), que incorpora otros serotipos diferentes, al tiempo que excluye algunos de los serotipos cubiertos por VNC previas (3, 6A/C, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 15A, 15B/C, 16F, 17F, 20, 23A, 23B, 24F, 31 y 35B) [10,11]. Finalmente, se han publicado resultados en un estudio en adultos fase 1-2 de otra vacuna 24-valente (VNC24) que utiliza una tecnología diferente a las otras VNC y que incluye los serotipos 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F y 33F [12].

El objetivo de este estudio fue analizar la evolución de los serotipos de *S. pneumoniae* en función de su perfil de inclusión en diferentes vacunas conjugadas (ya utilizadas en el pasado [VNC7], presentes [VNC10 y VNC13], nuevas [VNC15 y VNC20] y en preparación para el futuro [VNC21 y VNC24]) así como los patrones fenotípicos de susceptibilidad antimicrobiana asociados, aislados en el Hospital Universitario de Getafe (HUG) durante 2008-2022.

MÉTODOS

Se estudiaron 313 cepas de *S. pneumoniae* causantes de ENI aisladas en el HUG (650 camas; cobertura para 230.000 habitantes) desde enero de 2008 a diciembre de 2022 en muestras normalmente estériles (sangre, líquido cefalorraquídeo, líquido ascítico, líquido articular, líquido pleural, absceso de endometrio y líquido ótico obtenido por timpanocentesis). Los resultados fueron analizados en periodos de cinco años (2008-2012; 2013-2017 y 2018-2022) y de manera global, correspondiendo a los 15 años. Todas estas cepas fueron enviadas al Laboratorio Regional de Salud Pública de la Comunidad de Madrid (LRSP-CM), en el contexto del sistema de Vigilancia de ENI como enfermedad de declaración obligatoria (EDO). La identificación del serotipo se llevó a cabo mediante el test de aglutinación por látex (Pneumotest-latex) y la reacción de Quellung usando antisueros comerciales (Statens Serum Institut; Dinamarca). Se estudió la sensibilidad a penicilina, eritromicina y levofloxacino, determinando la concentración mínima inhibitoria (CMI) mediante un método de difusión en gradiente de concentración (E-test) en agar Müller Hinton suplementado con un 5% de sangre de oveja (bioMérieux España, S.A). De acuerdo a los puntos de corte EUCAST para penicilina, las cepas fueron categorizadas como sensibles (CMI < 0,06 mg/L), sensibles cuando se incrementa la exposición (CMI > 0,06 mg/L - 2 mg/L) y resistentes (CMI > 2 mg/L). En el caso de eritromicina, según criterios EUCAST, aquellas cepas con CMI < 0,25 mg/L y CMI > 0,5 mg/L fueron categorizadas como sensibles o resistentes respectivamente. En cuanto al antibiótico levofloxacino, según criterios EUCAST, aquellas cepas con CMI < 0,001 mg/L, CMI 0,001 mg/L- 2 mg/L y CMI > 2 mg/L fueron clasificadas como sensibles a dosis estándar, sensibles cuando se incrementa la dosis de exposición y resistentes, respectivamente. Se calcularon los valores de concentración que inhiben el crecimiento de > 50% y > 90% de los aislados (CMI_{50} y CMI_{90}) para los antibióticos estudiados. Para la comparación de variables cualitativas se empleó la prueba exacta de Fisher, considerando significativos los valores de $p < 0,05$.

RESULTADOS

Ciento veinticinco de las 313 cepas estudiadas fueron aisladas en el periodo 2008-2012, 100 en el periodo 2013-2017 y 88 en el periodo 2018-2022. La evolución del porcentaje de serotipos de *S. pneumoniae* aislados durante 2008-2022 se muestra en la Figura 1.

Los niveles de cobertura de serotipos por las diferentes vacunas conjugadas consideradas en este trabajo se exponen en la Figura 2. Los 6 serotipos más frecuentes a lo largo de todo el estudio fueron: 8, 3, 19A, 1, 11A y 22F que representan respectivamente 42, 41, 20, 18, 13 y 12 del total de cepas analizadas. La frecuencia de serotipos incluidos en las vacunas VNC7, VNC10, VNC13, VNC15, VNC20 y VNC24 disminuyeron significativamente en el periodo 2013-2017 respecto al periodo inicial 2008-2012, pasando de ser respectivamente para cada una de ellas del 13,6% al 5,0%, del 36,0% al 8,0%, del 59,2% al 30,0%, del 63,2% al 36,0%, del 76,8% al 63,0% y del 76,8% al 63,6%. En el caso concreto de la VNC15 la disminución del segundo periodo (2013-2017) al tercero (2018-2022) también resultó significativa, con un descenso del 36,0% al 20,4%. Contrariamente, la proporción de serotipos cubiertos por la VNC21 se incrementó de forma significativa desde 2008-2012 a 2013-2017, con un aumento del 64,0% al 77,0%.

A lo largo de cada periodo, más del 50% de todas las cepas se correspondieron únicamente con 6 serotipos, encontrándose el resto en baja proporción. La Tabla 1 muestra la distribución de los 6 serotipos más frecuentes en cada periodo y de forma global, en relación con su cobertura por diferentes vacunas conjugadas. Durante los años 2008-2012 los serotipos 3, 1, 19A, 7F, 6C y 11A supusieron en conjunto el 53,6% de los aislamientos. Entre 2013 y 2017 los serotipos 3, 8, 12F, 19A, 22F y 19F representaron el 51% de las cepas. Finalmente, a lo largo de 2018-2022 los serotipos 8, 3,11A, 15A, 4 y 6C incluyeron al 55,5% de los casos. En este último periodo, los serotipos 8 y 11A (cubiertos por la nueva VNC20, pero no por vacunas conjugadas previas) supusieron conjuntamente el 34 % de los aislamientos. Es este mismo quinquenio los serotipos adicionales 15A y 6C, incluidos en la VNC21 en desarrollo, pero no en otras vacunas conjugadas de menor cobertura, representaron de manera combinada el 8% de las cepas. El cambio de frecuencia desde el primer al segundo periodo del serotipo 1 y del 7F resultó significativo, con una caída del 12% al 3% y del 8,8% a 0% en cada caso. El serotipo 12F, pese a no estar cubierto por las vacunas conjugadas empleadas hasta el momento, disminuyó significativamente del 7% en 2013-2017 al 0% en 2018-2022. Por el contario, el serotipo 8 se incrementó significativamente desde el 2013-2017 pasando de un 11% a un 29,5% en 2018-2022.

En conjunto, 237 cepas (75,7%) se mostraron sensibles a penicilina, 71 (22,7%) sensibles cuando se incrementa la exposición y 5 resistentes (1,6%). Los valores de CMI50 y CMI90 de penicilina durante los 15 años de la serie fueron 0,023 mg/L y 0,75 mg/ L respectivamente. En el caso de eritromicina 248 cepas resultaron sensibles (79,2%), 1 cepa sensible cuando se incrementa la exposición (0,3%) y 64 cepas resistentes (20,4%) con niveles de CMI_{50} y CMI_{90} de 0,125 mg/L y >256 mg/L respectivamente. Finalmente, ningún aislamiento presentó sensibilidad a dosis estándar de levofloxacino, 302 mostraron sensibilidad a dosis incrementada (96,5%) y 11 (3,5%) fueron resistentes. La CMI_{50} y CMI_{90} para este antibiótico fue de 1 mg/

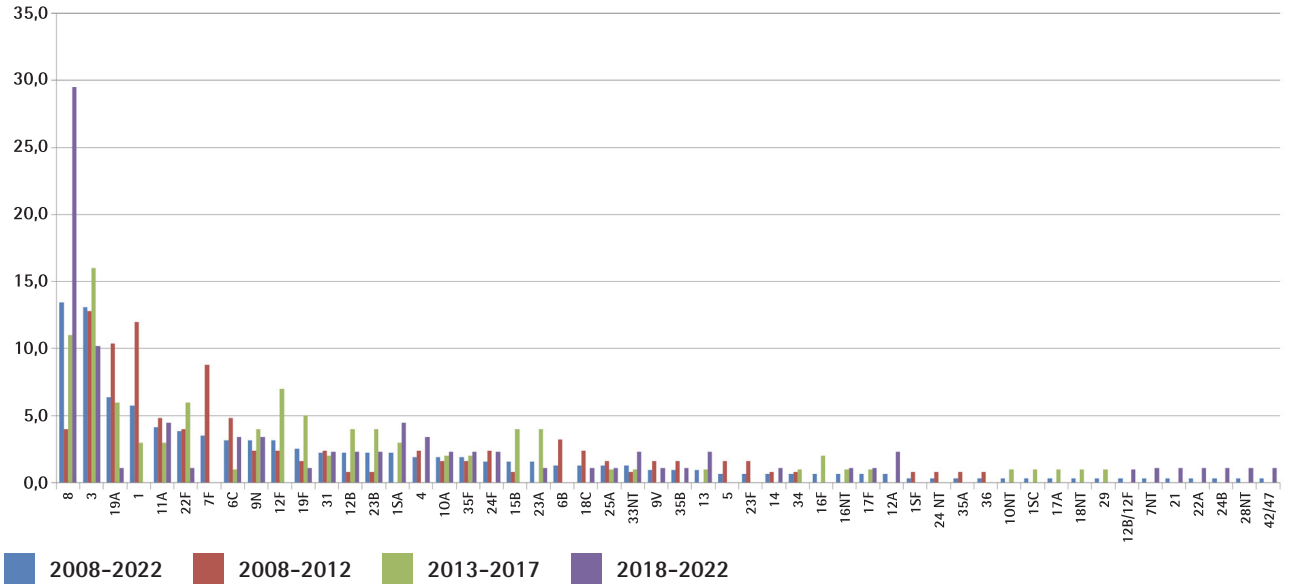

Figura 1 | **Evolución de los serotipos (%) de *S. pneumoniae* aislados en el HUG durante 2008-2022**

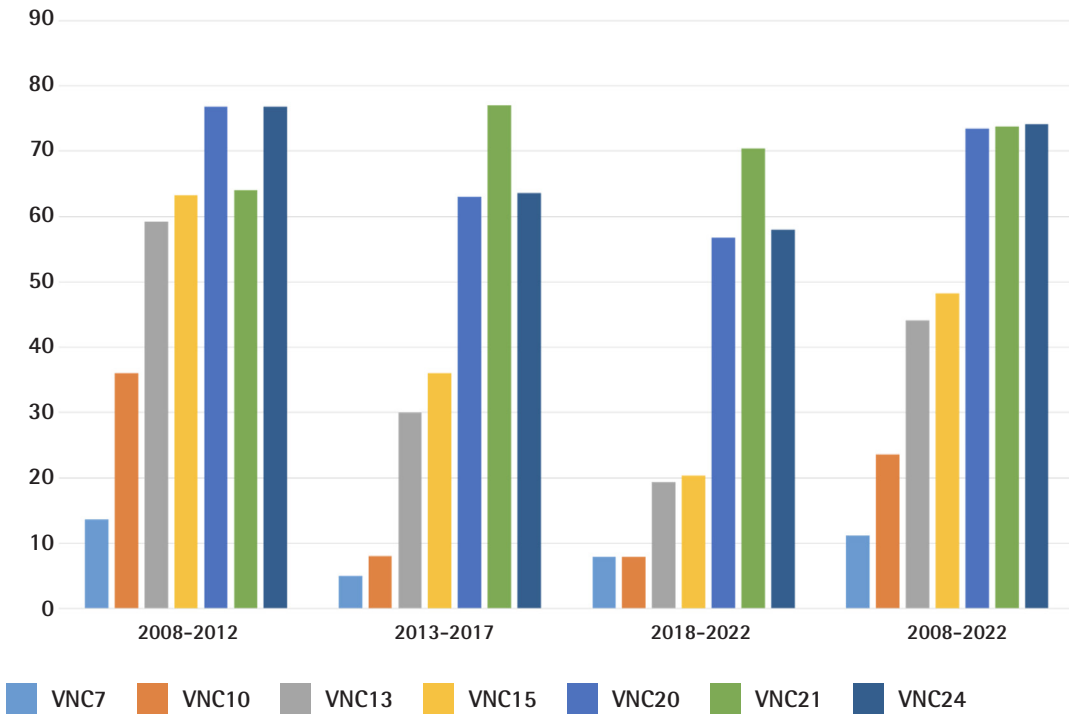

Figura 2 | **Cobertura potencial de las diferentes VNC (pasadas, presentes y futuras) según los periodos de estudio.**

L y 2 mg/L respectivamente. En la Tabla 2 se resumen los resultados de sensibilidad a penicilina, eritromicina y levofloxacino en función del periodo de aislamiento.

DISCUSIÓN

La introducción de vacunas conjugadas ha tenido un gran impacto en la epidemiología de la ENI y sus perfiles de sensibilidad antibiótica asociada [13,14, 15]. El descenso de la frecuencia de los serotipos vacunales ha sido acompañado de un aumento de los casos producidos por otros serotipos no incluidos en las vacunas conjugadas. Así, al comparar los dos primeros periodos de estudio, como consecuencia de la inclusión en el año 2010, de VNC13 en lugar de VNC7 en el calendario vacunal, se observó un descenso en la frecuencia de los nuevos serotipos cubiertos. El serotipo 1, principal causante de ENI en el primer periodo, descendió de forma significativa y muy acusada. Otros serotipos de la VNC13 también disminuyeron como el 19A y especialmente, el 7F, no aislándose ningún caso de este último serotipo a partir del primer periodo. No obstante, estos cambios se acompañaron de un aumento de otros serotipos no incluidos en VNC13 como son el serotipo 8 que alcanzó en el último periodo casi el 30% de los aislamientos. El aumento significativo de los serotipos cubiertos por la vacuna en desarrollo VNC21 puede reflejar un efecto de reemplazo por serotipos no cubiertos hasta el momento por este tipo de vacunas. El cambio en el calendario de vacunación del adulto en el año 2018 dado por la sustitución de la VNC23 por la VNC13, refuerza en el tercer periodo de estudio, los resultados ya obtenidos previamente por la inmunización infantil con esta vacuna. Sin embargo, pese al empleo de la VNC13 tanto en la población infantil como adulta, el serotipo 3 continúa siendo frecuente (no ha experimentado cambios significativos entre periodos, oscilando del 16% en 2013-2017 al 10,2 % en 2018-2022). El papel de VNC15 frente al serotipo 3 está en debate, se ha informado que esta vacuna induce una mayor capacidad fagocítica e inmunógena que la VNC13 [16]. Como se mencionó previamente, esta nueva vacuna esta aceptada para su uso pediátrico.

En el momento presente, se consideran dos opciones de vacunación del adulto con las nuevas VNC15 y VNC20. La pauta única con VNC20 o la pauta secuencial con VNC15 seguida de la VNP23 [17]. La primera de estas pautas es la que se ha incorporado al calendario de vacunación del adulto en la Comunidad de Madrid. Un dato a destacar es el notable incremento de la ENI asociada al serotipo 8 (aumento significativo del segundo al tercer periodo). Este serotipo no cubierto por la VNC13, ni por la VNC15, empezó a ser un serotipo emergente en España y en el resto de Europa en años anteriores, llegando a constituir en la actualidad el principal serotipo responsable de ENI en el HUG [13]. Junto con el serotipo 8, se observó en el último periodo de estudio un menor incremento del serotipo 11A (no alcanzó significación esta-

Tabla 1 **Datos de los 6 serotipos más frecuentes por periodo**

2008-2022			2008-2012			2013-2017			2018-2022		
Serotipos	Inclusión en Vacunas conjugadas	N (%)	Serotipos	Inclusión en Vacunas conjugadas	N (%)	Serotipos	Inclusión en Vacunas conjugadas	N (%)	Serotipos	Inclusión en Vacunas conjugadas	N (%)
8	VNC20, VNC21, VNC24	42 (13,4%)	3	VNC13, VNC15, VNC20, VNC21, VNC24	16 (12,8%)	3	VNC13, VNC15, VNC20, VNC21, VNC24	16 (16%)	8	VNC20, VNC21, VNC24	26 (29,5%)
3	VNC13, VNC15, VNC20, VNC21, VNC24	41 (13,1%)	1	VNC10, VNC13, VNC15, VNC20, VNC24	15 (12%)	8	VNC20, VNC21, VNC24	11 (11%)	3	VNC13, VNC15, VNC20, VNC21, VNC24	9 (10,2%)
19A	VNC13, VNC15, VNC20, VNC21 VNC24	20 (6,4%)	19A	VNC13, VNC15, VNC20, VNC21 VNC24	13 (10,4%)	12F	VNC20, VNC21, VNC24	7 (7%)	11A	VNC20, VNC21, VNC24	4 (4,5%)
1	VNC10, VNC13, VNC15, VNC20, VNC24	18 (5,8%)	7F	VNC10, VNC13, VNC15, VNC20, VNC21, VNC24	11 (8,8%)	19A	VNC13, VNC15, VNC20, VNC24	6 (6%)	15A	VNC21	4 (4,5%)
11A	VNC20, VNC21, VNC24	13 (4,2%)	6C	VNC21	6 (4,8%)	22F	VNC15, VNC21	6 (6%)	4	VNC10, VNC13, VNC15, VNC20, VNC24	3 (3,4%)
22F	VNC15, VNC21	12 (3,8%)	11A	VNC20, VNC21, VNC24	6 (4,8%)	19F	VNC7, VNC10 VNC13, VNC15, VNC20, VNC21, VNC24	5 (5%)	6C	VNC21	3 (3,4%)

***En cada uno de los tres quinquenios se indican los 6 serotipos que supusieron más del 50% de todos los serotipos identificados, según su cobertura por diferentes vacunas conjugadas. Para el total del estudio los 6 serotipos más frecuentes representaron en conjunto el 46,7% de los aislamientos.**

dística), tampoco cubierto por las vacunas hasta ahora disponibles (ni por la VNC15), pero si por la VNC20. Otros serotipos también de interés son el 15A y el 6C (ambos incluidos en la nueva VNC21, pero no en otras vacunas conjugadas). No obstante, el posible papel que desempeñen en el futuro las nuevas vacunas en desarrollo está por aún por definir. La VNC21, si bien incorpora nuevos serotipos no considerados en otras vacunas conjugadas, excluye al mismo tiempo algunos de los serotipos cubiertos por VNC previas. Este hecho quizá pudiera suponer un riesgo potencial de reaparición de serotipos ya en descenso (1, 4, 5, 6B, 9V, 19F, 23F). No obstante, estos aspectos deberán ser, en su caso, evaluados en el futuro. Entre los nuevos serotipos cubiertos por la VNC24; 2, 17F, y 20B son por el momento poco frecuentes. Sólo el 9N es relativamente relevante en la Comunidad de Madrid [18].

Por último, en relación a los patrones fenotípicos de susceptibilidad antimicrobiana, cabe destacar una disminución de resistencia a penicilina en el último periodo (CMI90 cuatro veces menor en este tercer periodo con respecto al primero), posiblemente como resultado del uso de la VNC13, que como se ha indicado presenta cobertura frente al serotipo 19A, uno de los serotipos asociados en años previos a mayor tasa de resistencia a penicilina [19]. No obstante, en este último periodo (2018-2022), como ya se ha comentado también comienza a observarse un aumento del serotipo 11A. Este serotipo está actualmente asociado con resistencia a penicilina [15, 20].

Una limitación de este estudio radica en que el periodo total de tiempo se dividió en quinquenios para intentar agrupar un número relativamente amplio de cepas para su comparación. Sin embargo, los años 2018-2019 se corresponden a la fase tardía post-VNC13 mientas que, en los años 2020, 2021 y 2022 el número de casos de ENI pudo verse claramente influido y alterado como resultado de efectos asociados con la pandemia (medidas de contención, sobrecarga sanitaria asistencial, infra-diagnóstico y sub-notificación). Este hecho pudo suponer un efecto artefacto en los resultados observados. Como conclusión, nuestro estudio muestra una reducción importante en la frecuencia de la ENI ocasionada por serotipos incluidos en VNC13 en nuestro entorno asistencial. Sin embargo, están emergiendo serotipos no cubiertos por esta vacuna, lo que señala el interés que puedan representar otras nuevas vacunas conjugadas en los próximos años y que pueden condicionar en el futuro de manera indirecta la evolución de los patrones de sensibilidad o resistencia.

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Tabla 2 **Resultados de sensibilidad a penicilina, eritromicina y levofloxacino.**

		2008-2012	2013-2017	2018-2022
Penicilina	Sensibles	89 (71,2%)	77 (77%)	71 (80,7%)
	Sensibles cuando se incrementa la exposición	35 (28%)	19 (19%)	17 (19,3%)
	Resistentes	1 (0,8%)	4 (4%)	0 (0%)
	CMI_{50} (mg/L)	0,023	0,023	0.023
	CMI_{90} (mg/L)	1	0,38	0,25
Eritromicina	Sensibles	95 (76%)	85 (85%)	68 (77,2%)
	Sensibles cuando se incrementa la exposición	0 (0%)	0 (0%)	1 (1,1%)
	Resistentes	30 (24%)	15 (15%)	19 (21,6 %)
	CMI_{50} (mg/L)	0,125	0,125	0,125
	CMI_{90} (mg/L)	>256	>256	>256
Levofloxacino	Sensibles a dosis estándar	0 (0%)	0 (0%)	0 (0%)
	Sensibles cuando se incrementa la exposición	119 (95,2%)	97 (97%)	86 (97,7%)
	Resistentes	6 (4,8%)	3 (3%)	2 (2,3%)
	CMI_{50} (mg/L)	1	1,5	1,5
	CMI_{90} (mg/L)	1,5	2	2

CONFLICTO DE INTERESES

Juan Carlos Sanz ha asistido a reuniones científicas, congresos y ponencias con financiación de Pfizer. El resto de autores declaran no tener ningún conflicto de intereses.

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Evolución temporal de la terapia antirretroviral (2017-2021): análisis de la modificación del tratamiento y su impacto económico

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RESUMEN

Objetivos. Analizar las modificaciones de la terapia antirretroviral (TAR) y su impacto económico en la práctica clínica diaria.

Material y métodos. Estudio observacional, retrospectivo de los pacientes que iniciaron TAR entre 01/2017-12/2021 (seguimiento hasta 12/2022). Variables recogidas: TAR, duración, motivo del cambio y costes del tratamiento.

Resultados. 280 pacientes iniciaron TAR. La mediana de durabilidad de la 1ª línea fue: 19,9 meses en 2017 (IC95% 13,9-25,9), 12,2 meses en 2018 (IC95% 4,7-19,7), 27,4 meses en 2019 (IC95% 6,8-48,1) y no se alcanzó la mediana para los años 2020 y 2021 (p<0,001). De un total de 541 líneas prescritas, la triple terapia con inhibidores de la proteasa se modificó en el 63,8% (81/127), seguido de los inhibidores de la integrasa 52,1% (159/305), mientras que, la terapia dual (DTG/3TC) solo en el 8,3% (7/84). De un total de 261 modificaciones, la simplificación/optimización 47,5% (124/261) fue el principal motivo, seguido de efectos adversos 21,8% (57/261), siendo el 2017 el único año donde ambos motivos se encontraban al mismo nivel. El impacto económico de los cambios supusieron una reducción del coste medio de 34,0€ [-391,4 a +431,4] al mes/paciente. El año 2019 es el único año donde estos cambios se asociaron con un incremento del coste adicional medio (23,4€ [-358,3 a +431,4]).

Conclusiones. Dejando atrás el fracaso virológico, la simplificación a regímenes de un solo comprimido y de mayor tolerancia han marcado la nueva la era TAR. Con un impacto económico que, a pesar del punto de inflexión del 2019, refleja una reducción progresiva de costes mantenida en el tiempo.

Palabras Clave: terapia antirretroviral, virus de la inmunodeficiencia humana, modificación, impacto económico.

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Temporal evolution of antiretroviral therapy (2017-2021): analysis of treatment change and its economic impact

ABSTRACT

Objectives. To analyze the modifications of antiretroviral therapy (ART) and their economic impact on daily clinical practice.

Material and methods. Observational, retrospective study of patients who started ART between 01/2017-12/2021 (follow-up until 12/2022). Variables collected: prescribed ART, duration, the reason for the change, and treatment costs.

Results. A total of 280 patients initiated ART therapy. The median durability of 1st line was: 19.9 months in 2017 (95%CI 13.9-25.9), 12.2 months in 2018 (95%CI 4.7-19.7), 27.4 months in 2019 (95%CI 6.8-48.1) and the median was not reached for the years 2020 and 2021 (p<0.001). Triple therapy with protease inhibitors was changed in 63.8% (81/127) of cases, followed by integrase inhibitors 52.1% (159/305), while dual therapy (DTG/3TC) only in 8.3% (7/84). The main cause of discontinuation was simplification/optimization 47.5% (124/261), followed by adverse effects 21.8% (57/261), with 2017 being the only year where simplification/optimization was at the same level as adverse effects. The economic impact of ART changes resulted in an average cost reduction of 34.0€ [-391.4 to +431.4] per month per patient. The year 2019 stands out as the only year where these changes were associated with an increase in mean additional cost (23.4€ [-358.3 to +431.4]).

Conclusions. Optimization/simplification accounts for almost half of the reasons for TAR change, with an economic impact that, despite the inflection point of 2019, each year manages to exceed the previous one, achieving a progressive cost reduction maintained over time.

Keywords: antiretroviral therapy, human immunodeficiency virus, modification, economic impact.

INTRODUCCIÓN

Desde la aparición de la terapia antirretroviral (TAR) la evolución de la infección por el virus de la inmunodeficiencia humana (VIH) ha cambiado radicalmente, se ha reducido de forma consistente la morbi-mortalidad, alcanzando una esperanza de vida prácticamente normal y mejorando la calidad de vida de los pacientes.

Con el paso de los años se dispone de un gran arsenal terapéutico cada vez más innovador, reflejado en el cambio de paradigma del reto clínico: anteriormente los cambios estaban impulsados por el fracaso a la terapia [1], ahora se buscan cambios que nos lleven al fármaco ideal en base a otras características: mejor tolerancia, menos interacciones, pautas de administración más cómodas, optimización fármaco-económica.

Hoy en día, las recomendaciones de inicio en un paciente VIH incluyen pautas de 2 o 3 fármacos [2]. Las pautas triples incluyen dos inhibidores de la transcriptasa inversa análogos de los nucleósidos (ITIAN) con un tercer fármaco (un inhibidor de la transferencia de cadena de la integrasa (INI), un inhibidor de la transcriptasa inversa no nucleósido (ITINN) o un inhibidor de la proteasa con ritonavir (IP/r)), y la pauta doble un ITIAN (lamivudina) con un INI (dolutegravir). No obstante, en los últimos años la guía GeSIDA incluye los INI como tercer fármaco en todas las pautas que recomienda como preferentes, dejando al resto de grupos como pautas alternativas; esto se debe a la elevada eficacia de los INI, que, junto con una mejor tolerancia, un menor perfil de interacciones e incluso una mayor rapidez, logran la supresión virológica en comparación con otras pautas [2,3].

Respecto al impacto económico que han supuesto estos cambios en las tendencias de uso de TAR, una revisión sistemática realizada en 5 países europeos ya nos mencionaba la falta de estudios sobre costes de esta patología [4]. El último estudio anual de costes en función de las recomendaciones de la guía GeSIDA es del año 2018, por lo que no incluía la combinación bictegravir/emtricitabina/tenofovir alafenamida (comercializado en España en 2019) la cual ahora es una de las pautas preferentes, así como la terapia dual dolutegravir/lamivudina, coformulado que parece minimizar los costes [5].

Nos encontramos en un escenario donde conviven fármacos antiguos de los que ya disponemos de su genérico, con nuevos coformulados recomendados como pautas preferentes y cuyos precios varían, suponiendo diferencias de más de 200 euros mensuales en el precio de las terapias de inicio [2].

En este contexto de una continua variación en las tendencias de uso de TAR, y la importancia de conocer el impacto económico que supone por la cronicidad de la patología, planteamos este estudio llevado a cabo en la práctica clínica diaria de un hospital de tercer nivel, con el objetivo principal de analizar la evolución temporal de la modificación del TAR y los motivos que han llevado a ello y, como objetivo secundario, determinar si estamos consiguiendo un incremento del ahorro económico asociado a estos cambios.

MATERIAL Y MÉTODOS

Estudio observacional y retrospectivo de los pacientes diagnosticados de infección por VIH que iniciaron su primer tratamiento antirretroviral entre enero del 2017 y diciembre del 2021. Se excluyeron a los pacientes sin seguimiento tras el inicio del TAR.

Las variables recogidas fueron género, edad, TAR de inicio, cambio de TAR y su motivo, y la duración del tratamiento TAR anterior. Todos los pacientes que continuaron con TAR tuvieron un seguimiento hasta el 31/12/2022.

Los regímenes de TAR incluidos son: inhibidores de la transcriptasa inversa análogos de nucleósidos (ITIAN), inhibidores de la transcriptasa inversa no nucleósidos (ITINN), inhibidores de la proteasa (IP) e inhibidores de la integrasa (INI).

La variable resultado principal fue la durabilidad del TAR, definida como: tiempo hasta que se interrumpió o modificó el tratamiento.

Las causas de discontinuación se clasificaron en las siguientes categorías: simplificación/optimización (incluye el cambio a una pauta de menor complejidad o a una incluida como preferente por las principales guías de VIH), efectos adversos (EA), intolerancia, fracaso virológico, interacción farmacológica, embarazo, desconocido o pérdida de seguimiento.

Por último, para evaluar el impacto económico de estas modificaciones, se calculó, por paciente, la diferencia del coste mensual entre el esquema TAR después de la modificación y el esquema TAR previo al cambio, y se hizo una media de los costes individuales para ver el impacto global.

La identificación de los pacientes se realizó en la consulta de atención farmacéutica de la Unidad de Pacientes Externos, de forma que se registraba tanto los inicios como los cambios de TAR. El resto de las variables se recogieron de la historia clínica electrónica.

Para el análisis económico se utilizó el programa *Farmatools Dominion® Dispensación a Pacientes Externos* (DPE) que proporciona el precio actualizado del fármaco en el momento concreto en que se dispensó.

El análisis estadístico se realizó con SPSS Statistics22®. Para la estadística descriptiva, las variables cualitativas se describieron mediante porcentajes y se realizó la prueba de Chi-cuadrado; para las cuantitativas se utilizaron medidas de tendencia central y se realizó la prueba t-student.

Se realizaron curvas de supervivencia para el análisis de la durabilidad mediante el método de Kaplan-Meier, dando las medianas de supervivencia con su intervalo de confianza (IC) al 95% y se compararon las curvas mediante la prueba log rank, con un nivel de significación de $p<0,05$.

El estudio fue aprobado por el Comité Ético de Investigación Clínica de Aragón (referencia PI22/051).

Tabla 1 **Características basales de los pacientes con relación a la modificación de la terapia antirretroviral.**

	Total de pacientes (N=280)	Pacientes con cambio TAR (N=156)	Pacientes sin cambio TAR (N=124)	Valor P
Edad (media ± DE)	41,2 ± 11,0	42,3 ± 10,9	39,8 ± 10,9	p=0,063
Género				p= 0,789
Masculino	162 (57,9%)	91 (56,2%)	71 (43,8%)	
Femenino	118 (42,1%)	66 (56,0%)	52 (44,0%)	
Año de inicio TAR				p< 0,001
2017	69 (24,6%)	64 (92,8%)	5 (7,2%)	
2018	55 (19,6%)	46 (83,6%)	9 (16,4%)	
2019	64 (22,9%)	35 (54,7%)	29 (45,3%)	
2020	50 (17,9%)	10 (20,0%)	40 (80,0%)	
2021	42 (15,0%)	2 (4,8%)	40 (95,2%)	
Esquema TAR**				p< 0,001
2 ITIAN + 1 INI	175 (62,5%)	97 (55,4%)	78 (44,6%)	
2 ITIAN + 1 IP	73 (26,1%)	54 (74,0%)	19 (26,0%)	
1 ITIAN + 1 INI	27 (9,6%)	4 (14,8%)	23 (85,2%)	
Tipo de ITIAN				p< 0,001
ABC/3TC	23 (8,2%)	19 (82,6%)	4 (17,4%)	
TAF/FTC	143 (51,1%)	58 (40,6%)	85 (59,4%)	
TDF/FTC	87 (31,1%)	74 (85,1%)	13 (14,9%)	
Nº comprimidos/día				p< 0,001
1	187 (66,8%)	75 (40,1%)	112 (59,9%)	
≥2	93 (33,2%)	82 (88,2%)	11 (11,8%)	

ABC: abacavir; DE: desviación estándar; FTC: emtricitabina; INI: inhibidores de la proteasa; IP: inhibidores de la integrasa, ITIAN: inhibidores de la transcriptasa inversa análogos de nucleósidos; TAR: terapia antirretroviral; TAF: tenofovir alafenamida; TDF: tenofovir disoproxil; 3TC: Lamivudina

***Todos los resultados están expresados en nº de pacientes (porcentaje), a excepción de la edad.**

****** **El esquema 2 ITIAN + 1 ITINN no ha sido incluido por tener solo 5 pacientes**

RESULTADOS

Durante el periodo de estudio un total de 280 pacientes iniciaron terapia antirretroviral, el 57,9% de ellos eran hombres y la media de edad fue 41,2 ±11,0 años. En la tabla 1 se divide a los pacientes en 2 grupos en función de si modifican o no su TAR de 1ª línea, y se detallan las características basales de ambos grupos.

Al final del estudio 92 (32,9%) pacientes continuaban con el primer TAR prescrito. El 44,6% de los pacientes llevó solo una línea de TAR, el 29,6% 2 líneas y el 25,7% 3 o más líneas. La mediana de duración de un fármaco antirretroviral hasta su modificación (independientemente de la línea de prescripción en la que se utiliza) fue de 32,3 meses (IC95% 28,9-36,2) y, al estratificar por líneas, la mediana de duración de la primera línea TAR fue ligeramente inferior (28,8 meses, IC95%:24,1-33,5).

La mediana de durabilidad del primer TAR por año fue: 19,9 meses en 2017 (IC95% 13,9-25,9), 12,2 meses en 2018 (IC95% 4,7-19,7), 27,4 meses en 2019 (IC95% 6,8-48,1) y no se alcanzó la mediana para los años 2020 y 2021 (p<0,001).

Al estratificar en función del tipo de esquema TAR inicial también se han encontrado diferencias estadísticamente significativas (28,7 meses para 2 ITIAN + 1 INI (IC95% 23,2-34,2), 16,4 meses para 2 ITIAN + 1 IP (IC95% 9,9-22,9) y no se alcanzó con la pauta dual 1 ITIAN + 1 INI (p=0,002)); así como para el número de comprimidos de la pauta TAR: 1 comprimido/día vs ≥2comprimidos/día (38,9 meses (IC95% 34,9-42,9), vs 5,0 meses (IC95% 3,8-6,3) respectivamente, p<0,001). La durabilidad tan escasa de los regímenes VIH con ≥2comprimidos/día

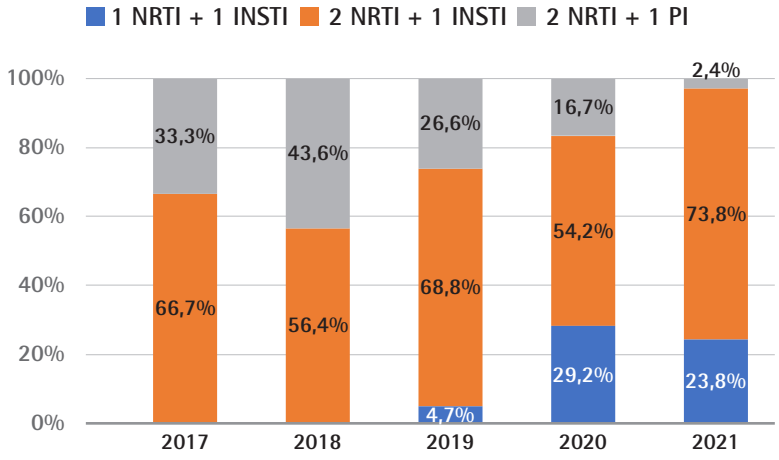

Figura 1 Tendencia temporal en la prescripción de régimen antirretroviral de primera línea

INI: inhibidores de la proteasa; IP: inhibido res de la integrasa, ITIAN: inhibido res de la transcriptasa inversa análogos de nucleósidos.

*El esquema 2 ITIAN + 1 ITINN no ha sido incluido por tener solo 5 pacientes

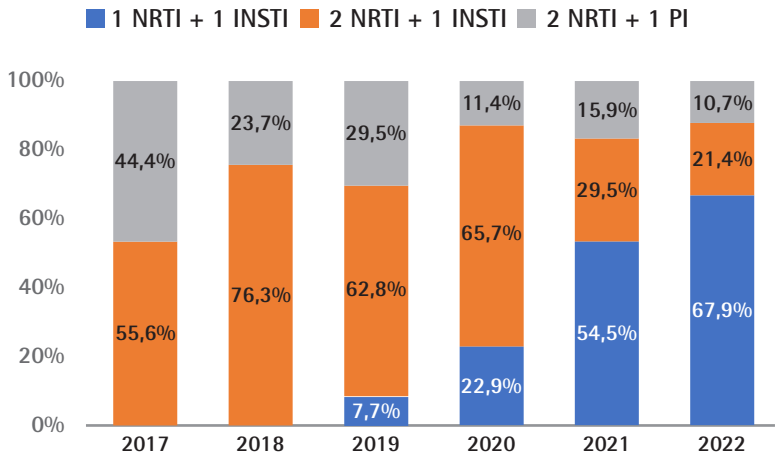

Figura 2 Tendencia temporal en la prescripción del régimen antirretroviral de segunda y posteriores líneas.

INI: inhibidores de la proteasa; IP: inhibido res de la integrasa, ITIAN: inhibidores de la transcriptasa inversa análogos de nucleósidos.

*Otros esquemas TAR no han sido incluidos por tener menos de 10 pacientes.

estuvo impulsada por la simplificación en más de la mitad de los casos (52,4% [43/82]), seguido de los efectos adversos/intolerancia (26,8% [22/82]).

En total se prescribieron 541 líneas TAR, en las figuras 1 y 2 se muestra la tendencia temporal en el tipo de TAR prescrito de 1ª línea así como en líneas posteriores respectivamente.

La proporción de regímenes de un solo comprimido (STR, *single tablet* regimen) prescritos en 1ª línea fue de un 36,7%

Tabla 2 **Tipos de cambios en el esquema TAR realizados en el periodo 2019-2022**

	CAMBIO A**				
ESQUEMA DE PARTIDA*	ABC/3TC/DTG	BIC/FTC/TAF	DRV/c/FTC/TAF	DTG/3TC	TDF/FTC+RAL
ABC/3TC/DTG (n=36)	-	2,0	3,0	12,6	0,5
BIC/FTC/TAF (n=16)	0,5	-	1,5	3,5	2,5
DRV/c/FTC/TAF (n=25)	1,0	4,0	-	6,6	1,0
EVG/c/FTC/TAF (n=38)	-	16,7	0,5	2,0	-
TDF/FTC+DRV/c (n=24)	0,5	1,0	8,1	1,5	1,0
TDF/FTC+DTG ó RAL (n=25)	5,1	4,5	1,5	1,5	-
OTROS (n=16)	2,0	0,5	3,5	1,0	1,0
TOTAL	9,1	28,8	18,2	28,7	6,1

ABC: abacavir; BIC: bictegravir; c: cobicistat; DRV: darunavir; DTG: dolutegravir; EVG: elvitegravir; FTC: emtricitabina; RAL: raltegravir; TAF: tenofovir alafenamida; TDF: tenofovir disoproxil; 3TC: lamivudina

***Porcentajes hechos respecto a los cambios totales realizados entre 2019-2022 (n=198)**

****Se han excluido aquellos esquemas TAR con porcentajes de cambio <5%**

en 2017 y aumentó a un 52,4% en el año 2019; no obstante, el mayor incrementó fue a partir del año 2020, superando el 95%.

Con un total de 261 modificaciones (incluyendo todas las líneas de prescripción), la principal causa de discontinuación fue la simplificación/optimización (47,5%), seguido de efectos adversos (21,8%), fracaso virológico (9,2%) y embarazo (7,3%); el resto de las causas representan un porcentaje menor al 5%.

Si lo desglosamos por años, en todos ellos el principal motivo fue la simplificación/optimización, excepto para el año 2017, donde dicho motivo se encontraba al mismo nivel que las modificaciones por EA.

De los 3 principales esquemas TAR, la combinación de 2ITIAN+ 1IP se modificó en el 63,8% de los casos, seguido de 2ITIAN+ 1INI (52,1%). La terapia dual (1 ITIAN+1 INI) solo se modificó en el 8,3% de las prescripciones.

En la tabla 2 se muestra los tipos de cambio realizados en el periodo de tiempo 2019-2022.

Respecto a los EA, de los 57/261 que han sido motivo de cambio, destaca en primer lugar la afectación renal (17/57) siendo tenofovir disoproxilo el causante de 12 de ellos; en segundo lugar los efectos gastrointestinales (12/57), la mitad de ellos asociados a los IP, seguido de la afectación psiquiátrica (8/57) propia de los INI.

En cuanto al fracaso virológico, el 87,5% (21/24) de los casos se produjeron en la primera etapa del estudio (entre los años 2017-2019). Más de la mitad de ellos (62,5%) no llevaban prescrito ninguno de los esquemas TAR recomendados actualmente como preferentes, siendo el esquema DRV/C/FTC/TAF el más frecuente (29,2%) (con un inhibidor de la proteasa potenciado como tercer fármaco). A pesar de que para este primer periodo de estudio no teníamos implantado aún el cálculo de la adherencia del paciente según las dispensaciones en el área de pacientes externos del servicio de farmacia, en los casos donde ha sido posible estimarla, la media de adherencia de dichos pacientes ha sido de un 91,1% ± 22,7, presentando una adherencia <95% el 55,6% (10/18) de los pacientes.

Si se tiene en cuenta solo los fármacos de primera línea, de los 156 pacientes que modificaron su TAR, la discontinuación por simplificación/optimización fue ligeramente mayor (55,5%), resultando interesante ver cómo de los 123 pacientes que modificaron su TAR antes de alcanzar la mediana de durabilidad de 1ª línea, a pesar de que el motivo con mayor impacto sigue siendo la simplificación (53,0%), los efectos adversos/intolerancia también tuvieron un peso importante (30,4%). Además, en este subgrupo de pacientes, si estratificamos por tipo de TAR, el principal fármaco que se modificó con el objetivo de simplificar fue un régimen basado en inhibidor de la integrasa (TAF/FTC + DTG) representando el 41,0% de este motivo de cambio, en contraposición del fármaco que más se modificó a causa de los EA o intolerancia, que supone en este caso el 48,6% y se basa en un inhibidor de la proteasa (TAF/FTC + DRV/c).

En el gasto económico asociado a la prescripción de estos fármacos, se observa una tendencia de descenso en el coste del TAR, a pesar de tener un repunte en el año 2019. De esta forma, el precio medio/mes por paciente y año es el siguiente: 648,3€ [136,5-806,9] en 2017, 510,1€ [330,1-758,7] en 2018, 547,4€ [369,9-981,6] en 2019, 515,9€ [388,5-592,8] en 2020, y 495,3€ [359,8-717,0] en 2021.

El impacto económico de los cambios de TAR realizados durante el periodo de estudio supusieron una reducción del coste medio de 34,0 € [-391,4 a +431,4] al mes por paciente. En la figura 3 se muestra el impacto económico de los cambios según el año en el que se ha realizado dicho cambio.

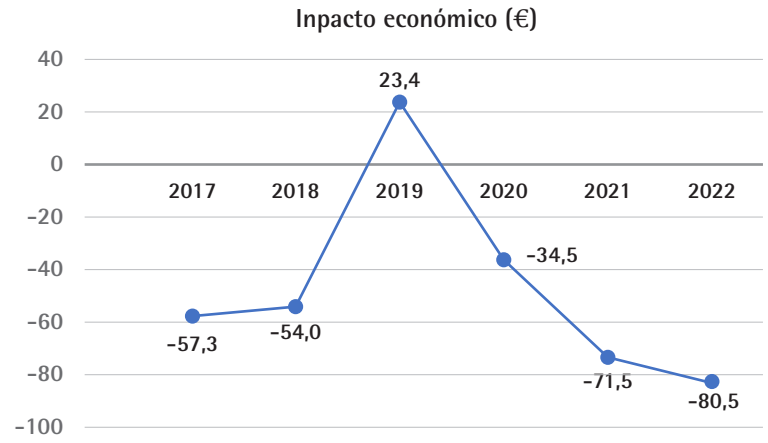

Figura 3 | **Impacto económico de las modificaciones del esquema TAR por año (reducción o incremento del coste medio al mes por paciente)**

DISCUSIÓN

En este estudio retrospectivo describimos la evolución de la terapia antirretroviral en los últimos 5 años. Si analizamos estudios previos, como el de Korten et al. [6] donde analizaban los motivos de cambio de TAR de 1ª línea (2011-2017), la interrupción por intolerancia/toxicidad fue la principal causa, mismo resultado que el obtenido en el estudio de Sobrino-Jiménez C. [7] durante diciembre del 2014. En ambos estudios el esquema ITIAN más frecuente era el que contenía tenofovir disoproxil en su forma de sal de fumarato (TDF), destacado por su toxicidad renal y ósea, y, a pesar de que estas toxicidades ya venían descritas en las guías, no fue hasta el 2018 cuando la guía geSIDA [8] menciona en sus recomendaciones de esquemas preferentes el uso únicamente de la forma tenofovir alafenamida (TAF). La otra clase TAR más utilizada como acompañante de los ITIAN era los ITINN, como efavirenz, caracterizado por su toxicidad en el sistema nervioso central [9].

Nuestro estudio muestra un panorama diferente, más actualizado, donde la familia de los ITINN como fármaco de inicio ya apenas se utiliza, y donde se refleja como los INI van ganando terreno a los IP, de forma que, en 2019, los IP ya no representan ni un tercio de las prescripciones en 1ª línea, coincidiendo con la aparición de los INI de segunda generación (bictegravir y dolutegravir en pauta dual) [10].

Este cambio de escenario implica nuevas recomendaciones de prescripción y logran evitar los efectos adversos como principal motivo de discontinuación como veníamos viendo hasta ahora. Así, en nuestro estudio, vemos como el año 2017 fue el último donde los efectos adversos eran el principal motivo de cambio junto con la simplificación/optimización. A partir de ahí la simplificación/optimización logra el primer puesto para el resto de los años, mismo resultado que el obtenido en el estudio de Nunzia et al. [11], llevado a cabo desde el 2014 al 2020.

Respecto al fracaso virológico como motivo de cambio, vemos cómo el desarrollo de nuevas combinaciones TAR más eficaces, más cómodos de administrar al ser en su mayoría STR, además del cálculo automático de la adherencia en base a las dispensaciones realizadas desde el servicio de farmacia han logrado, con el paso de los años, que los cambios por dicho motivo hayan disminuido notablemente, quedando casos muy puntuales.

La durabilidad de la terapia es otro reflejo de este cambio, en los estudios donde la principal causa de modificación es la toxicidad, la durabilidad del TAR de primera línea lo encontramos en torno al año [12], año y medio [13], en contraposición de nuestro estudio, donde supera los 2 años (28,8 meses, IC95% 24,1-33,5). Además, este estudio muestra en sí mismo la evolución con los años, como para el 2017 la durabilidad de 1ª línea aún estaba en torno al año y medio, para el 2018 fue de tan solo 12 meses (justificada por la aparición en 2019 de nuevos coformulados que inducían a la modificación) y ya, para el año 2020, observamos como todavía ni se ha alcanzado la mediana de durabilidad.

Para apoyar la justificación de la corta durabilidad de los fármacos prescritos en 2018 debido a los cambios realizados en el 2019 por la aparición de nuevos coformulados (BIC/FTC/TAF y DRV/c/FTC/TAF), vemos como estos fármacos resultaron el 68,8% (22/32) de los cambios, partiendo como fármaco de inicio del FTC/TAF + DRVc en el 50,0% de los casos (11/22) y del coformulado EVG/c/TAF/FTC en el 27,3% (6/22).

Un concepto muy importante, y en el que se ha incidido más en los últimos años, es en el desarrollo de regímenes de un solo comprimido, ya que es la estrategia más eficiente para evitar la mala adherencia, y con ello el desarrollo de resistencias y el fracaso virológico [14]. En este estudio la prescripción de TAR de 1ª línea con esquemas basados en ≥2 comprimidos se producen entre los años 2017-2019, otorgando una mediana de durabilidad que no alcanza un semestre y motivado (en

la mitad de los casos) por la necesidad de simplificar la pauta. Es a partir del año 2020 cuando se logra superar el 95% de las prescripciones de 1ª línea de tipo STR, cumpliendo así con la recomendación de las guías de práctica clínica.

Un gran avance fue la aparición de la terapia dual DTG/3TC, dos medicamentos coformulados que ofrecen la misma eficacia, con un mayor perfil de tolerancia y a un precio menor respecto a otras pautas de referencia [15]. Este fármaco innovador apareció por primera vez en las guías en el año 2019, pero no fue hasta el año 2020 [16] cuando nuestra guía nacional lo incluyó como pauta preferente. En una cohorte nacional realizada entre 2014-2020 [17], fue en el año 2020 cuando la prescripción de DTG/3TC aumentó a 1/4 de todos los tratamientos iniciales. En nuestro estudio, para el mismo año, vemos que ya supera el 1/4 de los tratamientos iniciales (29,2%), pero lo que realmente destaca es, que más de la mitad de los cambios realizados en el 2021 y 2022 fueron a DTG/3TC. Además, el buen perfil de seguridad y tolerabilidad lo vemos reflejado en las tasas de modificación, que fueron tan solo en el 8,3% de los casos.

Acerca del impacto económico, se manifiesta una diferencia llamativa en el año 2019 respecto al resto. Como se ha mencionado anteriormente, en este año apareció bictegravir/emtricitabina/tenofovir alafenamida, un nuevo coformulado como pauta preferente, este fármaco no solo cobró importancia como prescripción de 1ª línea, sino que representa el esquema preferente de cambio en el periodo de años 2019-2022. En el estudio de Guitérrez-lorenzo M et al. [18], llevado a cabo entre 03/2019-10/2020, destacan como el cambio a BIC/FTC/TAF supuso un aumento económico del 9,3%. En nuestro estudio el aumento observado en 2019 podría justificarse por los cambios realizados a BIC/FTC/TAF, así como al coformulado DRV/c/FTC/TAF, que apareció a mediados del 2018 y el cual, a pesar de no ser una pauta preferente, parece la preferida cuando se quiere cambiar a un esquema basado en inhibidores de la proteasa como se observa en la tabla 2.

Además, hemos observado como el cambio a uno de estos dos nuevos coformulados de TAF, tenía como fármaco de partida esquemas que incluían fármacos genéricos, como el TDF o la combinación de TAF/FTC, lo que acentúa un mayor coste. No obstante, estos cambios estaban justificados por beneficio clínico que llevan asociado, el evitar la aparición de los efectos adversos propios del TDF, así como fomentar el uso de STR, que a posteriori se ven reflejados en la adherencia [14].

Siguiendo la línea del tiempo, vemos que la diferencia de coste medio/mes por paciente disminuyó un 9,5% en el año 2021 respecto al año 2019, favorecido principalmente por el aumento de la prescripción de la terapia dual DTG/3TC, mismo resultado que el obtenido en el estudio de Krentz HB et al. [19]. Si lo comparamos con el año 2017, la disminución llega a ser de un 23,6%.

Este estudio está limitado por su carácter retrospectivo y monocéntrico, el hecho de recoger los motivos de cambio de forma retrospectiva puede afectar a su exactitud.

Como conclusiones, este estudio comprende un periodo de 5 años donde la terapia VIH ha evolucionado de forma significativa. Con nuevos esquemas más simplificados y económicos, se ha conseguido que la toxicidad como motivo de cambio pase a un segundo plano, y que el impacto económico asociado a las modificaciones realizadas desde el año 2020 vayan a favor de la sostenibilidad del sistema sanitario.

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CONFLICTO DE INTERÉS

Los autores declaran no tener ningún conflicto de interés.

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Coinfección bacteriana en el paciente COVID-19 crítico: incidencia, impacto y necesidad de tratamiento antibiótico

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RESUMEN

Objetivos. Evaluar la frecuencia de coinfección bacteriana al ingreso en UCI en pacientes con neumonía por SARS-CoV-2, su microbiología e impacto en el pronóstico. El objetivo secundario fue identificar factores de riesgo de coinfección al ingreso.

Métodos. Estudio retrospectivo, se incluyeron pacientes con neumonía por SARS-CoV-2 ingresados en UCI. Definimos coinfección bacteriana por síntomas respiratorios, datos radiológicos, resultados microbiológicos positivos y clínicamente significativos en muestras obtenidas en las primeras 48 h de ingreso y/o una determinación de procalcitonina ≥ 0,5 ng/mL en las primeras 48 h. Evaluamos variables demográficas, comorbilidades, datos de la infección por SARS-CoV-2, *scores* de gravedad, tratamientos recibidos, necesidad de soporte respiratorio y resultados (estancia y mortalidad durante el ingreso en UCI y hospital).

Resultados. Se analizaron 182 pacientes, 62 (34.1%) con coinfección bacteriana. La microbiología más frecuente fue *S. pneumoniae* y *M. pneumoniae*. El 96.1% de los pacientes recibieron antibioterapia al ingreso, 98,9% corticoides, 27,5% tocilizumab y 7,7% remdesivir. El 85.7% necesitó ventilación mecánica invasiva. La puntuación en SOFA (OR: 1,315, IC 95% 1,116-1,548) y el retraso en el ingreso en UCI (OR: 0,899, IC 95% 0,831-0,972) se relacionaron con el riesgo de coinfección. La coinfección bacteriana aumenta el riesgo de muerte en el hospital (OR 2,283; IC 95% 1,011-5,151; p=0,047).

Conclusiones. La coinfección bacteriana es frecuente en pacientes COVID ingresados en UCI y aumenta el riesgo de muerte. No es posible identificar con seguridad, en el momento de ingreso, qué pacientes no se benefician de tratamiento antibiótico.

Palabras clave: Covid-19; Sepsis; SDRA; antibiótico, neumonia

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Bacterial coinfection in the critically-ill COVID-19 patient: incidence, impact and need for antimicrobial therapy

ABSTRACT

Objectives. To assess the frequency of bacterial coinfection upon ICU admission in SARS-CoV-2 pneumonia patients, its microbiology, and impact on prognosis.The secondary objective was to identify risk factors for coinfection on admission.

Methods. Retrospective study, including patients with SARS-CoV-2 pneumonia admitted to the ICU.We defined bacterial coinfection by respiratory symptoms, radiological data, positive and clinically significant microbiological results in samples obtained in the first 48 h of admission and/or a determination of procalcitonin ≥ 0.5 ng/mL in the first 48 h.We evaluated demographic variables, comorbidities, SARS-CoV-2 infection data, severity scores, treatments received, need for respiratory support and outcomes (ICU and hospital mortality).

Results. A total of 182 patients were analyzed, 62 (34.1%) with bacterial coinfection.The most frequent microbiology was S. pneumoniae and M. pneumoniae.96.1% of the patients received antibiotic therapy on admission, 98.9% corticosteroids, 27.5% tocilizumab, and 7.7% remdesivir.85.7% required invasive mechanical ventilation.The SOFA score (OR: 1.315, 95% CI 1.116-1.548) and the delay in ICU admission (OR: 0.899, 95% CI 0.831-0.972) were related to the risk of coinfection.Bacterial coinfection increases the risk of death in hospital (OR 2.283; 95% CI 1.011.5.151; p=0.047).

Conclusions. Bacterial coinfection is common in COVID patients admitted to the ICU and increases the risk of death.It is not possible to identify with certainty, at the time of admission, which patients do not benefit from antibiotic treatment.

Keywords: Covid-19; Sepsis; ARDS; antibiotic, pneumonia

INTRODUCCIÓN

A fecha de 12 de abril de 2023, cuando han transcurrido poco más de 3 años desde su irrupción, se han registrado cerca de 800 millones de casos y de 7 millones de muertes en todo el mundo por el virus SARS-CoV-2 [1].

Los primeros meses de la pandemia supusieron un desafío para la Medicina Intensiva. En primer lugar, la sobrecarga de pacientes desbordó la capacidad de las UCI en todo el mundo [2,3]. En segundo lugar, no se disponía de un tratamiento respaldado por la evidencia, lo que provocó un aluvión de publicaciones de distintos documentos de recomendaciones y propuestas que rápidamente quedaron desactualizadas [4–6].

Uno de los aspectos que continúa generando debate es la necesidad de tratamiento antibiótico en los pacientes con COVID que ingresan en UCI por insuficiencia respiratoria.

Con la información de la gripe de 1918-1919, en la que la coinfección bacteriana participaba en la mayoría de las muertes [7] o de la pandemia de influenza del 2009, en la que se identificó un 30.3% de coinfección bacteriana al ingreso en UCI, asociada con una mortalidad significativamente mayor [8]; se recomendó iniciar tratamiento antibiótico empírico hasta descartar la coinfección. La coinfección bacteriana es infrecuente entre los pacientes hospitalizados por COVID-19 [9,10] pero, entre los pacientes que ingresan en UCI las incidencias son muy variables, desde el 5,5% hasta el 46% [11–15].

Nuestro objetivo principal es analizar la coinfección bacteriana al ingreso en UCI: incidencia, microbiología e impacto en el pronóstico. El objetivo secundario es evaluar si es posible identificar a los pacientes con coinfección en el momento del ingreso en UCI.

MATERIAL Y MÉTODOS

Estudio retrospectivo realizado en una UCI de un hospital universitario de segundo nivel que atiende una población aproximada de 300000 habitantes. Se incluyeron los pacientes mayores de 18 años ingresados por insuficiencia respiratoria secundaria a neumonía por SARS-CoV-2, diagnosticada mediante PCR, desde marzo de 2020 a diciembre de 2021. Se excluyeron los pacientes en los que se detectó una PCR positiva para SARS-CoV-2 sin neumonía. En caso reingreso únicamente se analizó el primer episodio.

El estudio fue aprobado por el CEIC de Galicia (código CEIC 2021/450)

Evaluamos variables demográficas (sexo y edad), comorbilidades, datos de la infección por SARS-CoV-2 (días de enfermedad al ingreso, tiempo hasta negativización de la PCR), *scores* de gravedad (APACHE II y SOFA), tratamientos recibidos, necesidad de soporte respiratorio (oxigenoterapia de alto flujo -OAF-, ventilación mecánica no invasiva -VMNI- y ventilación mecánica invasiva -VM-) y resultados (estancia y mortalidad durante el ingreso en UCI y hospital).

Las comorbilidades se analizaron a partir de la historia clínica del paciente y se evaluaron siguiendo el Índice de comorbilidad de Charlson.

La coinfección bacteriana se definió por la presencia de síntomas respiratorios, datos radiológicos y resultados microbiológicos (hemocultivos, cultivos respiratorios, antigenuria de *Legionella* o *S. pneumoniae*, serología de neumonías atípicas, PCR de muestras respiratorias) positivos y clínicamente significativos en una muestra obtenida en las primeras 48 h de ingreso en UCI o antes del ingreso en UCI y/o la determinación de un nivel de procalcitonina (PCT) ≥ 0,5 ng/mL en las primeras 48 h de estancia en UCI. En aquellos pacientes en los que no se pudo obtener una muestra respiratoria para realización de PCR, se realizó determinación de IgG e IgM de *M. pneumoniae*, *C. pneumoniae*, *Legionella* y *C. burnetti*; en ausencia de otro resultado microbiológico positivo, se interpretó la elevación de IgM como diagnóstica.

Definimos tratamiento antibiótico adecuado a aquel en que se comprobó su actividad *in vitro* mediante antibiograma. En las neumonías atípicas se consideró tratamiento adecuado si el paciente recibió un macrólido o una quinolona.

Las variables continuas se expresan como mediana y p25-p75, las variables cualitativas como número y %. Para comparar medianas, empleamos el test U de Mann-Whitney y para comparar porcentajes Chi^2. Empleamos la regresión logística para evaluar la relación entre cada variable y la coinfección y la mortalidad durante el episodio de hospitalización. Se asumió un error **a** de 0,05.

RESULTADOS

Durante el periodo de estudio, ingresaron en nuestra UCI 182 pacientes por insuficiencia respiratoria secundaria a neumonía por SARS-CoV-2.

Un total de 62 (34,1%) pacientes cumplieron los criterios de coinfección bacteriana al ingreso. Las características de los pacientes, comparando la cohorte con coinfección (C) y sin coinfección (NC) se muestran en la tabla 1.

El 98,9% de los pacientes recibieron corticoides, el 27,5% tocilizumab (41,7% en NC y 9,7% en C, p<0,001), y el 7,7% remdesivir. Un 85,7% de los pacientes necesitaron ventilación mecánica invasiva y, de éstos, el 80,1% ventilación en prono.

No encontramos diferencias en cuanto a incidencia de sobreinfección o NAVM entre pacientes con o sin coinfección bacteriana (sobreinfección: C 54,8%, NC 45,8%, p=0,249; NAVM: C 36,9%, NC 34,2%, p=0,544).

De los 62 pacientes clasificados como coinfectados, 28 tuvieron resultados microbiológicos positivos y 34 fueron incluidos debido a la elevación de PCT. El APACHE II y el SOFA al ingreso de los pacientes con microbiología positiva fue 12,50 (10,00-15,75) y 5 (3,25-7,00), respectivamente; mientras que, entre los pacientes incluidos por la elevación de PCT, el APACHE II fue de 15,00 (10,00-20,00) y el SOFA de 6,00 (4,00-8,00), De los 28 pacientes con microbiología positiva, 10 fallecieron durante el ingreso (35,7%), mientras que de los 34 con micro-

Tabla 1 **Características de la población y comparación de la cohorte con coinfección y sin coinfección bacteriana.**

	Población			p
	Global n= 182	No coinfección n=120	Coinfección bacteriana n=62	
Sexo (mujer)	50 (27,5)	34 (28,3)	16 (25,8)	0,717
Edad (años)	67,0 (56,75, 73,00)	67,00 (56,00, 74,00)	67,00 (57,00, 73,00)	0,963
Inicio ss-ingreso hospital (d)	7,00 (4,00, 9,00)	7,00 (5,00, 9,00)	6,00 (3,00, 7,25)	<0,001
Inicio ss-ingreso UCI (d)	9,00 (6,75, 11,00)	9,00 (7,00, 12,00)	8,00 (5,00, 11,00)	0,007
Estancia hospital preUCI (d)	1,00 (0,00, 4,00)	1,00 (0,00, 4,00)	1,00 (0,00, 4,00)	0,761
Estado vacunacional				
Vacunación completa al ingreso	16 (8,8)	15 (12,5)	1 (1,6)	0,014
Vacunación incompleta	8 (4,4)	5 (4,2)	3 (4,8)	0,834
No vacunación	152 (83,5)	97 (80,8)	55 (88,7)	0,175
Comorbilidades				
Hipertensión arterial	101 (55,5)	64 (53,3)	37 (59,7)	0,414
Dislipemia	84 (46,2)	58 (48,3)	26 (41,9)	0,412
Diabetes mellitus	38 (20,9)	21 (17,5)	17 (27,4)	0,119
Cardiopatía	32 (17,6)	22 (18,3)	10 (16,1)	0,711
Enf pulmonar	44 (24,2)	28 (23,3)	16 (25,8)	0,712
Enf neurológica	27 (14,8)	18 (15,0)	9 (14,5)	0,931
Enf renal crónica	16 (8,8)	8 (6,7)	8 (12,9)	0,159
Enf hepática	16 (8,8)	11 (9,2)	5 (8,1)	0,803
Neoplasia hematológica	13 (7,1)	7 (5,8)	6 (9,7)	0,340
Neoplasia sólida	18 (9,9)	11 (9,2)	7 (11,3)	0,649
Arteriopatía periférica	22 (12,1)	18 (15,0)	4 (6,5)	0,094
Trasplante de órganos sólido	4 (2,2)	2 (1,7)	2 (3,2)	0,497
Inmunosupresión	18 (9,9)	10 (8,3)	8 (12,9)	0,328
Índice Charlson	1,00 (0,00-2,00)	1,00 (0,00-2,00)	1,00 (0,00-2,25)	0,334
Scores de gravedad al ingreso				
APACHE II	11,00 (8,00- 15,00)	10,00 (8,00- 14,00)	13,00 (10,00- 19,00)	0,001
SOFA	4,00 (3,00-6,00)	4,00 (3,00-5,00)	6,00 (4,00-8,00)	<0,001
Tratamiento recibido				
Corticoides	180 (98,9)	120 (100)	60 (98,4)	0,160
TCZ UCI 1 dosis	34 (18,7)	33 (27,5)	1 (1,6)	<0,001
TCZ UCI 2 dosis	16 (8,8)	16 (13,6)	0 (0)	0,002
TCZ planta o UCI	56 (27,5)	50 (41,7)	6 (9,7)	<0,001
Antibiótico primeras 48 h	175 (96,1)	113 (94,2)	62 (100)	0,052
Duración antibiótico inicial (d)	6,00 (5,00, 8,00)	6,00 (5,00, 8,00)	7,00 (5,00, 8,00)	0,369
Pico PCT	0,20 (0,10, 0,50)	0,10 (0,05, 0,20)	1,05 (0,50, 2,37)	<0,001

Tabla 1 **Características de la población y comparación de la cohorte con coinfección y sin coinfección bacteriana (cont.)**

	Población			p
	Global n= 182	No coinfección n=120	Coinfección bacteriana n=62	
Soporte respiratorio				
OAF < 24 h	46 (25,3)	32 (26,7)	14 (22,6)	0,548
OAF > 24 h	50 (27,5)	38 (31,7)	12 (19,4)	0,078
VMNI < 24 h	25 (13,7)	14 (11,7)	11 (17,7)	0,259
VMNI > 24 h	14 (7,7)	11 (9,2)	3 (4,8)	0,299
VM	156 (85,7)	98 (81,7)	58 (93,5)	0,030
VM al ingreso	127 (69,8)	78 (65,0)	49 (79,0)	0,051
Días VM	16,00 (6,00, 27,00)	15,00 (5,00, 26,00)	19,00 (7,00, 27,25)	0,104
Ventilación en prono	125 (68,7)	77 (64,2)	48 (77,4)	0,068
Resultados				
Negativización PCR en UCI	123 (67,6)	82 (68,3)	41 (66,1)	0,763
Estancia UCI (d)	19,50 (10,00, 31,00)	18,50 (10,00, 30,00)	22,00 (12,50, 33,25)	0,320
Estancia hospital (d)	33,00 (18,00, 52,25)	33,00 (18,00, 53,00)	31,00 (18,75, 49,00)	0,969
Mortalidad UCI	32 (17,6)	13 (10,8)	19 (30,6)	0,001
Mortalidad hospital	39 (21,4)	18 (15,0)	21 (33,9)	0,003

d: días, IOT: intubación orotraqueal, OAF: oxigenoterapia de alto flujo, PCT: procalcitonina, ss: síntomas, TCZ: tocilizumab, VM: Ventilación mecánica, VMNI: ventilación mecánica no invasiva,

biología negativa, fueron 11 (32,3%) los que fallecieron durante el ingreso.

Entre los pacientes con resultados microbiológicos positivos, *S. pneumoniae* y *M. pneumoniae* fueron la etiología más frecuente (17,8% cada una), seguidas por *K. pneumoniae* y *C. pneumoniae* (14,2% cada una) y *S. aureus* (10,7%). El 78.9% de los pacientes recibieron un macrólido, el 54,3% una cefalosporina de 3º generación, 24,6% se trataron con ceftarolina, mientras que se empleó linezolid y un meropenen/imipenen en el 18,3% cada uno. Entre los pacientes con coinfección, 4 (6,4%) recibieron un tratamiento antibiótico inicial inadecuado, y en 34 (54,8%) el tratamiento no pudo ser evaluado debido a que los resultados microbiológicos fueron negativos.

La tabla 2 muestra la relación entre cada variable y la coinfección (análisis univariante) y en la tabla 3 se presenta el análisis multivariante.

La estancia media en UCI fue de 19,50 (10,00-31,00) días y la hospitalaria 33,00 (18,00-52,25) días, con una mortalidad en UCI del 17,6% y hospitalaria de 21,4%. La presencia de coinfección bacteriana al ingreso (tal y como la hemos definido), es un factor de riesgo de mortalidad independiente de factores como inmunosupresión, scores de gravedad, estancia hospitalaria previa al ingreso en UCI, índice de Charlson, edad y necesidad de ventilación mecánica (OR 2,283; IC 95% 1,011-5,151; p=0,047) (Tabla 4).

DISCUSIÓN

La necesidad de VM (85,7%) es mayor que la descrita en los grandes estudios multicéntricos, que no alcanzan el 60% [12,16,10,17,18] pero comparable con la presentada en otros estudios unicéntricos de menor tamaño (con cifras que van desde el 73,2 al 94%) [11,13–15,19]. Los datos publicados de las UCI de nuestro entorno muestran una puntuación en SOFA y una necesidad de ventilación en prono similar a la nuestra [18,20], sin embargo, nuestra mortalidad fue de 17,6% en UCI y del 21,6% en el hospital, sensiblemente menor al 30% descrito en los estudios multicéntricos de nuestro país [17,18].

La incidencia de coinfección bacteriana al ingreso en UCI en nuestra serie fue del 34,1% y el 96,1% de nuestros pacientes recibieron tratamiento antibiótico en las primeras 48 horas. Entre pacientes hospitalizados, los estudios multicéntricos [10,21], las series unicéntricas [22–25] y los metaanálisis publicados han mostrado una tasa de cultivos positivos de entre 3,5 y 9,1% [9,26,27]. El porcentaje de pacientes con cultivos positivos al ingreso en UCI oscila entre el 5,5 y el 28% [11,12,14,15,19,25,28,29]. Sin embargo, debemos considerar ciertos factores que pueden influir en estos resultados. En primer lugar, la mayor parte de los estudios mencionados provienen del inicio de la pandemia, especialmente de la primera ola, y es muy probable que no se hayan realizado estudios microbiológicos en una gran parte de los pacientes: de 48.902

Tabla 2 **Factores de riesgo de coinfección. Análisis univariante**

	OR	IC 95%	p
Sexo femenino	0,880	0,440, 1,761	0,717
Edad	0,999	0,975, 1,024	0,960
Días de ss-ingreso hospital	0,860	0,785, 0,942	**0,001**
Días de ss-ingreso UCI	0,900	0,838, 0,967	**0,004**
Estancia hospital preUCI	0,984	0,907, 1,067	0,695
Vacunación completa	0,115	0,015, 0,890	**0,038**
Vacunación incompleta	1,169	0,270, 5,063	0,834
No vacuna	1,863	0,751, 4,621	0,179
Hipertensión arterial	1,295	0,696, 2,411	0,415
Dislipemia	0,772	0,416, 1,433	0,412
Diabetes mellitus	1,781	0,858, 3,696	0,121
Cardiopatía	0,857	0,377, 1,944	0,711
Enfermedad pulmonar	1,143	0,562, 2,322	0,712
Enfermedad neurológica	0,962	0,405, 2,288	0,931
Enfermedad renal crónica	2,074	0,739, 5,823	0,166
Enfermedad hepática	0,869	0,288, 2,623	0,804
Neoplasia hematológica	1,730	0,555, 5,389	0,345
Neoplasia sólida	1,261	0,463, 3,433	0,650
Arteriopatía periférica	0,391	0,126, 1,210	0,103
Trasplante de órgano sólido	1,967	0,270, 14,308	0,504
Inmunosupresión	1,630	0,609, 4,364	0,331
Índice de Charlson	1,111	0,908, 1,360	0,305
VM	3,255	1,069-9,914	**0,038**
VM al ingreso	2,030	0,991-4,159	0,053
APACHE II	1,112	1,047, 1,182	**0,001**
SOFA	1,352	1,159, 1,576	**<0,001**

pacientes hospitalizados en Reino Unido durante la primera ola, únicamente el 17,7% tienen muestras microbiológicas, aumentando al 30,5% entre los ingresados en UCI [16], y la incidencia de coinfección en el Hospital Clinic de Barcelona se multiplicó casi por tres al extender el periodo de estudio desde abril de 2020 a febrero 2021 [23,28]. Por otro lado, es frecuente que los cultivos sean negativos en pacientes en los que el diagnóstico de una neumonía bacteriana no ofrece dudas: en el ensayo clínico CAPE COD el 44,9% de los casos no tuvieron diagnóstico microbiológico [30]. En COVID, Coenen et al. han publicado que solo en el 29% de los casos clasificados por un panel de expertos como sospecha de coinfección se obtuvieron resultados microbiológicos positivos [31]. En nuestro estudio empleamos criterios clínicos, radiológicos, microbiológicos y biomarcadores para el diagnóstico de coinfección, estrategia empleada por otros autores que también publican cifras más elevadas; así, Baghdadi et al, en un estudio multicéntrico que incluyó 64.691 pacientes hospitalizados en EEUU, describen una incidencia del 18,5% [32]; y el panel de expertos del estudio de Karaba et al analizó más de 1.000 pacientes de 5 hospitales de EEUU considerando la presencia de coinfección probada en 1,18% de los pacientes hospitalizados y en el 3,4% de los pacientes ingresados en UCI, mientras que el 47,5% y el 64,4% de los pacientes (hospitalización convencional y UCI, respectivamente) cumplieron criterios de posible coinfección. En la serie de Liu et al, empleando un punto de corte de procalcitonina de 0,1 ng/mL, el 42,1% de los pacientes ingresados en el hospital cumplía criterios de coinfección bacteriana (hasta el 56,2% de los pacientes graves) [33].

En contraposición con otros estudios, en los que *S. aureus* es la bacteria identificada con más frecuencia, en UCI [11,14,15,24,29] y en planta [9,10,16], *S. pneumoniae*, *M. pneumoniae*, *K. pneumoniae* y *C. pneumoniae*, son las bacterias más frecuentes.

Nuestro porcentaje de cultivos positivos en el grupo de coinfectados (45,2%) no es muy distinto del descrito en otros estudios de neumonía [30] y es más alto que en otros estudios de COVID [31].

El uso de antibióticos en las primeras 24-48h entre los pacientes que ingresaron en UCI por neumonía por COVID es elevado, con porcentajes que oscilan entre 80,7 y 100% [11–13,19,29], cifras similares a nuestro caso, que alcanza el 96,1%. Fuera de UCI, los datos son más variables y van desde el 56,6% descrito por Vaughn et al [21] al 85,2% de los hospitales de Reino Unido [16]. La antibioterapia empleada coincide con la recomendada por las guías de tratamiento de neumonía adquirida en la comunidad [34,35].

La coinfección bacteriana es un factor de mal pronóstico entre pacientes COVID-19: Incremente la necesidad de ingreso en UCI [10] y la mortalidad, independientemente del ingreso en planta convencional [10,27,28,32,33] o UCI [15,29]. En nuestra serie, a pesar del elevado porcentaje de tratamiento antibiótico adecuado, la presencia de coinfección aumenta el riesgo de muerte durante el ingreso, independientemente de la edad, la gravedad, las comorbilidades y la presencia de inmunosupresión, del retraso en ingreso en UCI y de la necesidad de ventilación mecánica.

Recientemente ha habido una intensa discusión sobre el tratamiento antibiótico empírico precoz en la sepsis, que ha llevado al cambio de la recomendación de la *Surviving Sepsis Campaign* sobre el momento de inicio [36,37]. Los pacientes de nuestro estudio cumplen criterios de sepsis y de neumonía adquirida en la comunidad grave [35]. En ambas entidades, sepsis y neumonía, la indicación de tratamiento antibiótico está claramente establecida; sin embargo, actualmente las guías de tratamiento de COVID-19 recomiendan administrar tratamiento antibiótico solo en pacientes con sospecha de infección bacteriana [38–40], sin definir dicho concepto. La expectoración purulenta, la condensación radiológica con broncograma aéreo, el derrame pleural o la elevación significativa de PCT incrementan la probabilidad de infección bacteriana, pero no es posible confirmarla ni excluirla en base a dichos hallazgos [34].

Tabla 3 Factores de riesgo de coinfección. Análisis multivariante

	OR	IC 95%	p
Inicio ss-ingreso UCI (por día)	0,899	0,831, 0,972	**0,007**
Vacunación completa	0,172	0,021, 1,388	0,098
SOFA	1,315	1,116-1,548	**0,001**
VM al ingreso	1,297	0,588-2,858	0,519

Tabla 4 Factores de riesgo de mortalidad hospitalaria. Análisis multivariante

	OR	IC 95%	p
Coinfección bacteriana	2,283	1,011-5,151	**0,047**
Inmunosupresión	3,188	0,819-12,404	0,094
SOFA	1,077	0,909-1,277	0,391
APACHE II	1,016	0,938-1,101	0,700
Estancia hospitalaria preUCI	1,090	0,965-1,231	0,166
Índice de Charlson	0,987	0,729-1,338	0,934
Edad menor de 60 años	0,369	0,133-1,019	0,054
Necesidad de ventilación mecánica	2,619	0,494-13,880	0,258

Al igual que sugieren otros autores [34,41–43], acompañamos la administración de antibióticos con la obtención de muestras (sangre, esputo/aspirado traqueal/lavado broncoalveolar, orina) para estudios microbiológicas (hemocultivos, serología, cultivos respiratorios, PCR, antigenuria de *Legionella* y *S. pneumoniae*) y determinación al ingreso y diaria de PCT, con la intención de suspender el tratamiento antibiótico en las primeras 48 h de ingreso si la sospecha de coinfección bacteriana era baja (en base a evolución radiológica, resultados microbiológicos y evolución de la PCT). Es importante mencionar que el nivel de PCT ≥ 0,5 ng/mL fue establecido de forma retrospectiva, para clasificar los pacientes de cara al análisis, pero no se empleó como *trigger* de tratamiento.

Identificar los factores que predicen la presencia de coinfección al ingreso sería de gran ayuda para seleccionar a los pacientes que pueden beneficiarse del antibiótico y evitar efectos adversos inmediatos y a largo plazo en los que no [44]. Calderón-Parra et al, en base a opinión de expertos, establecieron las siguientes indicaciones "adecuadas" de tratamiento antibiótico empírico en pacientes COVID-19 ingresados en el hospital: sepsis, datos clínicos/analíticos/radiológicos de infección bacteriana, PCT ≥ 0,5 ng/mL o cultivos (significativos) positivos [44]. La saturación arterial ≤94%, los niveles de ferritina <338 ng/mL y la PCT >0,2 ng/mL son factores de riesgo independientes de coinfección en el paciente hospitalizado [23] y Bolker et al encontraron como predictores de coinfección la procedencia de un centro sociosanitario, la leucocitosis y la gravedad de la enfermedad [45]. No se ha validado una estrategia de tratamiento en base a estos resultados, y todos ellos incluyen algún factor como la gravedad o la insuficiencia respiratoria, presente en el paciente crítico, por lo que su utilidad parece limitada en nuestro ámbito; más aún, un metaanálisis estableció una relación entre la necesidad de ingreso en UCI o de VM y la presencia de coinfección [9]. Giannella et al elaboraron un score predictor, combinando el recuento de leucocitos, la puntuación en el índice de Charlson y los niveles de PCT, con un área bajo la curva ROC de 0,83 (0,75-0,90); cabe reseñar que una PCT ≥ 0,2 ng/mL clasifica al paciente como de alto riesgo y, siguiendo su recomendación, debería recibir tratamiento antibiótico [22]. En nuestra serie, los pacientes coinfectados ingresaron antes en UCI (respecto al inicio de los síntomas), necesitaron VM con mayor frecuencia y la puntuación en SOFA y APACHE II fue más elevada; haber recibido la pauta completa de vacunación fue un factor protector en el análisis univariante. En el análisis multivariante encontramos que cada punto en el SOFA score aumenta el riesgo (OR: 1,315, IC 95% 1,116-1,548) y que por cada día que transcurre desde el inicio de síntomas al ingreso en UCI el riesgo se reduce (OR: 0,899, IC 95% 0,831-0,972), datos con limitada utilidad clínica, claramente insuficientes para tomar decisiones terapéuticas.

El uso de la PCT para guiar el inicio y la duración del tratamiento antibiótico en las infecciones respiratorias se asocia con una menor mortalidad [46], sin embargo, su utilidad como *trigger* de tratamiento en casos de sepsis y NAC grave es más limitada, sugiriéndose su empleo para acortar la duración del tratamiento [34–36]. Existen dudas acerca de la capacidad de la PCT para predecir la presencia de infección bacteriana o si no es más que un marcador de gravedad en el COVID [47,48]. Moreno-García et al encontraron similares niveles de PCT en pacientes hospitalizados con y sin coinfección [23]; al igual que Elabbadi et al, en una serie de 101 pacientes COVID-19 críticos [14]; Atallah et al encontraron los valores basales de PCT eran más elevados en los pacientes que necesitaban ingreso en UCI o VM y en los que fallecían, pero también en los que presentaban bacteriemia o infección respiratoria [49]. Un punto de corte de PCT de 0,5 ng/mL tiene una sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo de 0,19-0,43, 0,72-0,89, 0,09-0,31 y 0,92-0,95, respectivamente, para el diagnóstico de coinfección bacteriana [23,49,50], y se ha propuesto no administrar tratamiento antibiótico en pacientes con una determinación basal ≤ 0,3 ng/mL al ingreso en UCI (valor predictivo negativo de 91,1%) [51]. Otras publicaciones únicamente establecieron una relación entre la PCT y la gravedad, relacionando su elevación por encima de 0,25 ng/mL con una mayor frecuencia de ingreso en UCI y de muerte entre pacientes hospitalizados [52] y una determinación ≥ 0,50nng/mL con una mayor mortalidad en UCI [51]. Por la metodología empleada, en nuestro estudio no podemos evaluar el rendimiento de la PCT para identificar pacientes con coinfección, al haberla incluido como criterio diagnóstico.

Nuestros resultados aportan información en un tema controvertido y no aclarado, de hecho, varias de las guías ac-

tuales no establecen recomendaciones a favor o en contra del tratamiento antibiótico en el paciente crítico con COVID-19 [40,53,54]. Siguiendo nuestra aproximación diagnóstica (criterios clínicos, radiológicos, analíticos y microbiológicos, y no únicamente microbiológicos) más de uno de cada tres pacientes ingresados en UCI por neumonía por SARS-CoV-2 cumple criterios de coinfección bacteriana, y presenta un mayor riesgo de muerte (al igual que se ha visto en la gripe). No hemos sido capaces de identificar variables que permitan decidir en qué pacientes es posible no administrar tratamiento antibiótico al ingreso con seguridad, pero nuestra estrategia se asocia con una baja mortalidad a pesar de la gravedad inicial de la población estudiada.

Nuestro estudio tiene varias limitaciones. Primero, se trata de un estudio unicéntrico y retrospectivo. Segundo, no se ha evaluado la aparición de resistencias a antimicrobianos durante el periodo de estudio, aunque los datos de nuestra UCI en el registro nacional de vigilancia de infección nosocomial (ENVIN) no muestran un aumento de las resistencias tras la pandemia (tasa de incidencia de multirresistencias durante los años 2018-2019: 3,63 por 1.000 estancias, años 2021-2022: 1,8 por 1.000 estancias). Tercero, nuestra metodología no nos ha permitido evaluar la capacidad de la PCT para identificar pacientes con coinfección. Cuarto, el elevado porcentaje de pacientes que recibieron tratamiento antibiótico no nos permite medir el impacto del mismo en el pronóstico. Quinto, no hemos analizado datos de las pruebas microbiológicas realizadas a nuestros pacientes, en general, se recogieron muestras de sangre, respiratorias y orina para realizar cultivos, serología, PCR y antigenurias, pero es muy posible que exista cierta variabilidad entre pacientes y, al mismo tiempo, la sobrecarga del Servicio de Microbiología pudo haber influido en el tipo de estudio realizado y en el retraso hasta obtener los resultados; por otro lado, el diagnóstico de neumonía atípica mediante serología es complejo y no se han realizado serologías de control en los pacientes que se han diagnosticado por este método. Sexto, es posible que alguno de los pacientes clasificados como coinfectados por la elevación de PCT no estuviera realmente coinfectado, sin embargo, como hemos comentado, el porcentaje de cultivos positivos del grupo de coinfectados es similar al descrito en otros estudios. Además, aunque la disfunción renal no fue muy frecuente entre nuestros pacientes, no se han valorado las cifras de PCT en relación a la función renal.

Como fortalezas, es uno de los pocos estudios que incluye pacientes más allá de las dos primeras olas de la pandemia y que no emplea únicamente criterios microbiológicos, además, incluimos un grupo de pacientes que ya han recibido al menos una dosis de alguna de las vacunas.

Para concluir, nuestros datos apoyan la hipótesis de que, entre pacientes COVID-19 con insuficiencia respiratoria severa, la coinfección bacteriana es frecuente y ensombrece el pronóstico, por lo tanto, a la espera de alguna herramienta que permita seleccionar con seguridad qué pacientes necesitan tratamiento antibiótico y cuáles no, debemos ser cautos a la hora de establecer recomendaciones en contra del mismo.

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CONFLICTO DE INTERÉS

Los autores declaran no tener ningún conflicto de interés.

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Original breve

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Evaluación de dos técnicas fenotípicas y un panel molecular multiplex comercial para la detección de diferentes carbapenemasas

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RESUMEN

Introducción. La prevalencia de enterobacterias productoras de carbapenemasas ha aumentado en los últimos años, considerándose un importante problema de salud pública.

Material y métodos. Se analizaron 106 muestras por distintas técnicas de detección de carbapenemasas: discos de inhibición (DI), test inmunocromatográfico (TIC) y una técnica genotípica, frente a una RT-PCR multiplex como método de referencia.

Resultados. Globalmente, las 3 técnicas superaron el 90% de sensibilidad, aunque con diferencias en el rendimiento de algunas de ellas por tipos de carbapenemasa. Los DI presentaron baja especificidad (62%) para OXA-48, mientras que con el TIC la sensibilidad para metalobetalactamasas tipo NDM (93%) fue ligeramente inferior que para OXA-48 (95%). Los mejores resultados se obtuvieron con la técnica genotípica (rendimiento global del 100%).

Conclusiones. A pesar de la menor sensibilidad de los TIC respecto a las técnicas moleculares, especialmente en carbapenemasas tipo NDM, con la modificación del protocolo conseguimos aumentar esta sensibilidad, y junto al menor precio, sencillez y rapidez convierte a esta técnica en una buena opción de screening.

Palabras clave: Carbapenemasas, diagnóstico, Enterobacterales.

Evaluation of two phenotypic techniques and a commercial multiplex molecular panel for the detection of different carbapenemases

ABSTRACT

Introduction. The prevalence of carbapenemase-producing Enterobacterales has increased in recent years and is considered an important public health problem.

Material and methods. A total of 106 clinical samples were analyzed by different carbapenemase detection techniques: inhibition discs (ID), immunochromatographic test (ICT) and a genotypic method, comparing them with a multiplex RT-PCR as a reference method.

Results. Overall, all 3 techniques exceeded 90% sensitivity, although with differences in the performance of some of them by carbapenemase type. DI had low specificity (62%) for OXA-48, while with TIC the sensitivity for NDM-type metallo-beta-lactamase (93%) was slightly lower than for OXA-48 (95%). The best results were obtained with the genotypic technique (100% overall performance).

Conclusions. Despite the lower sensitivity of TICs (especially in NDM carbapenemases) compared to molecular techniques, with the modification of the protocol we managed to increase this sensitivity and, together with the lower price, simplicity and speed, it makes this technique a good screening option.

Keywords: Carbapenemases, diagnosis, Enterobacterales.

INTRODUCCIÓN

En los últimos años la prevalencia de infecciones por enterobacterias productoras de carbapenemasas (EPC) se ha incrementado de manera significativa, por lo que un diagnóstico adecuado y precoz para adecuar el tratamiento puede tener gran importancia, especialmente en pacientes de alto riesgo

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Tabla 1 **Distribución de carbapenemasas por las distintas técnicas.**

Carbapenemasas	DI						TIC				BF				
	Sinergia con ADP + R TEM	Sinergia con ADP	Sinergia con BOR y ADP + R TEM	Sinergia con BOR + R TEM	R TEM	N	OXA-48	NDM	OXA 48/ NDM	N	OXA-48	NDM	OXA 48/ NDM	NDM/ VIM	N
OXA 48 (n=38)	0	0	4	2	31	1	37	0	0	1	38	0	0	0	0
NDM (n=36)	18	17	0	0	0	1	0	33	0	3	0	33	2	1	0
OXA 48/NDM (n=2)	2	0	0	0	0	0	0	1	1	0	0	1	1	0	0
Negativas (n=30)	0	0	0	0	0	30	0	0	0	30	0	0	0	0	30

DI: discos de inhibición; TIC: test inmunocromatográfico; BF: BioFire® BCID2; ADP: ácido dipicolínico; BOR: ácido borónico; R TEM: resistencia a temocilina; N: negativo.

[1]. Atendiendo a la clasificación molecular de Ambler, las más frecuentes son serin-carbapenemasas (Clase A), metalo-beta-lactamasas (MBL) de Clase B y las tipo OXA (Clase D) [2].

Tradicionalmente, para su diagnóstico los laboratorios han usado pruebas de inhibición con discos (DI), pero este método no es específico y presenta un tiempo medio de respuesta largo (24-48h) [3]. Por ello, a pesar de ser mucho más costosas, las pruebas moleculares se han considerado el "Gold standard". El panel comercial BioFire® BCID2 (BF) de bioMérieux es una PCR multiplex que integra extracción, amplificación y detección de patógenos y genes de resistencia, obteniendo resultados con sensibilidades y especificidades alrededor del 100% en aproximadamente hora y media [4].

En los últimos años, los test inmunocromatográficos (TIC) como el Coris Resist-4 O.K.N.V., han ganado terreno principalmente por la rapidez, siendo posible dar resultados en 15 minutos, con unos resultados de sensibilidad y especificidad cercanos al 100% [5].

En nuestro hospital, siguiendo la tendencia global, hemos observado un incremento en el diagnóstico de EPC, lo que nos ha llevado a implementar en cada momento aquellas técnicas disponibles más adecuadas. El objetivo de este estudio fue comparar 3 técnicas de detección de carbapenemasas frente a una PCR comercial considerada el método de referencia.

MATERIAL Y MÉTODOS

Durante dos años, se recogieron 106 cepas de enterobacterias pertenecientes a muestras clínicas de pacientes ingresados en nuestro hospital: 30 controles negativos y 76 EPC. Todas las muestras se procesaron siguiendo el procedimiento convencional de siembra e incubación. Las cepas se identificaron por MALDI-TOF Vitek®MS (bioMérieux) y se les realizó estudio de sensibilidad mediante el sistema comercial automatizado Vitek®2 (bioMérieux). Las concentraciones mínimas inhibitorias de carbapenémicos y ceftazidima/avibactam se evaluaron por tiras de gradiente (ETEST®bioMérieux y Liofilchem®MIC Test Strip, respectivamente).

A las 106 cepas se les realizaron todas las técnicas descritas a continuación.

a) Detección fenotípica con discos/inhibidores. Las suspensiones bacterianas equivalentes a un 0,5 McFarland se incubaron 18-20 horas en placas de Mueller-Hinton (bioMérieux) con un disco de 10 µg de meropenem, discos combinados con éste y diferentes inhibidores y un disco de 30 µg de temocilina (Rosco Diagnostica). La interpretación se realizó atendiendo a las guías EUCAST.

b) Allplex™Entero-DR Assay (Seegene Inc). Método de referencia en el que una suspensión de 2-3 colonias bacterianas junto con un control interno se sometió a una temperatura de 98ºC durante 10 minutos y una posterior centrifugación a 16.000g durante 2 minutos. Los sobrenadantes se usaron para la RT-PCR multiplex que detecta varios genes productores de carbapenemasas (bla-NDM, bla-KPC, bla-OXA-48, bla-VIM, bla-IMP) [6].

c) PCR multiplex BioFire®BCID2 Panel (FilmArrray®bioMérieux). Una suspensión bacteriana entre 0,5-1 McFarland se utilizó como muestra para la carga del cartucho según las indicaciones del fabricante. Entre sus dianas se incluyen genes que codifican carbapenemasas (IMP, KPC, OXA-48-like, NDM y VIM)

d) Método inmunocromatográfico Lateral Flow O.K.N.V. RESIST-4 (Coris BioConcept®, Belgium). Según recomendaciones del fabricante, las colonias se suspenden en el buffer incorporado en el kit y tras vortear, se añaden 3 gotas a cada cassette y se leen los resultados en 15 minutos. Para mejorar la visualización de las bandas débiles en carbapenemasas tipo MBL, se incorporó un paso previo adicional no descrito en la técnica de incubación a 35-37ºC durante 15 minutos tras la suspensión.

RESULTADOS

De las 106 muestras analizadas, 76 fueron positivas y pertenecían a 70 pacientes, 67% hombres (47/70) con una edad media de 67 años (30-94; IQR 18). Las carbapenemasas detectadas fueron tipo OXA-48 en el 50% de los casos (38/76), NDM en el 47% (36/76) y un 3% (2/76) de EPC que presentaban combinación de ambas carbapenemasas (OXA-48/NDM). En la Tabla 1 se muestran los resultados obtenidos con las distintas técnicas según el tipo de carbapenemasa.

Para conocer el rendimiento de cada técnica se tomó co-

Tabla 2 **Rendimiento de las distintas técnicas.**

Carbapenemasas	DI				TIC				BF			
	S	E	VPP	VPN	S	E	VPP	VPN	S	E	VPP	VPN
Global	97% [0,9-1,0]	58% [0,4-0,7]	77% [0,7-0,8]	94% [0,8-1,0]	95% [0,90-0,99]	100% [0,9-1,0]	100% [0,9-1,0]	88% [0,7-0,9]	100% [0,9-1,0]	100% [0,9-1,0]	100% [0,9-1,0]	100% [0,9-1,0]
OXA-48	97% [0,9-1,0]	62% [0,5-0,7]	69% [0,5-0,8]	97% [0,9-1,0]	95% [0,8-1,0]	100% [0,9-1,0]	100% [0,9-1,0]	94% [0,8-1,0]	97% [0,9-1,0]	94% [0,8-1,0]	95% [0,8-1,0]	97% [0,9-1,0]
NDM	97% [0,9-1,0]	88% [0,7-0,9]	90% [0,8-0,9]	97% [0,9-1,0]	93% [0,8-1,0]	100% [0,9-1,0]	100% [0,9-1,0]	91% [0,9-1,0]	100% [0,9-1,0]	97% [0,9-1,0]	97% [0,9-1,0]	100% [0,9-1,0]

DI: discos de inhibición; TIC: test inmunocromatográfico; BF: BioFire® BCID2; VPP: Valor Predictivo Positivo. VPN: Valor Predictivo

mo referencia el panel Entero-DR, obteniéndose de forma global una sensibilidad (S) del 97% para los DI, 95% para el TIC y un 100% para BF. Con respecto a la especificidad (E) y valor predictivo positivo (VPP) fueron del 100% para todas las técnicas, excepto para los DI (E=58%; VPP=77%). El valor predictivo negativo (VPN) fue del 94%, 88% y 100% para los DI, TIC y BF, respectivamente.

Estos mismos parámetros se estudiaron por tipo de carbapenemasa, observándose diferencias en el rendimiento de las técnicas (Tabla 2).

En el grupo de OXA-48, la E y VPP de los DI disminuyó por 18 cepas portadoras de NDM con resistencia a temocilina en las que no se confirmó la presencia de OXA-48. Además, se detectó un falso negativo (FN) en una *Klebsiella pneumoniae (*KP) OXA-48 en la que se apreciaba una doble población temocilina sensible con colonias dentro del halo. En las NDM, se encontró un FN en una KP-NDM y 4 falsos positivos (FP) por inhibición con los 2 inhibidores junto con resistencia a temocilina, confirmándose por PCR sólo la detección de OXA-48.

Para el TIC, la mayoría de los falsos negativos se obtuvieron en carbapenemasas de tipo NDM. Por otro lado, en las 17 cepas en las que no se aplicó el paso previo de calentamiento se obtuvieron 2 FN (KP-NDM y KP-OXA-48) y 5 NDM débiles, sin embargo, tras aplicar la incubación en 59 cepas, obtuvimos 2 FN en KP-NDM pero ningún resultado indeterminado, mostrando diferencias significativas respecto al grupo sin incubación ($p<0,05$).

DISCUSIÓN

Desde hace varios años las EPC se consideran un problema importante de salud pública [2] y posiblemente, la pandemia del SARS-CoV-2 haya agravado su diseminación por el uso excesivo de antibióticos de amplio espectro, el traslado de pacientes entre instituciones y el uso inapropiado de equipos de protección [7].

Con la existencia de nuevos antimicrobianos con perfiles únicos para el tratamiento de las distintas carbapenemasas, como la ceftazidima-avibactam activa frente a carbapenemasas tipo OXA-48 pero inactiva frente a MBL, gana peso la correcta identificación de las mismas [8]. Es por ello que técnicas rápidas como los TICs están siendo ampliamente implantadas en el medio hospitalario. Sin embargo, según nuestros resultados, este método presentó falsos negativos, especialmente en cepas portadoras de NDM, tal y como se describe en los ensayos de la propia técnica y en la literatura [9]. El paso previo de calentamiento de las cepas con el buffer de lisis descrito en este estudio mejoró sustancialmente la visualización de las bandas inmunocromatográficas, evitando confirmación con otras técnicas en un alto porcentaje, y con el consiguiente ahorro económico y disminución del tiempo de respuesta.

En la detección de OXA-48 mediante DI, la especificidad disminuyó un 38% debido al elevado número de cepas portadoras de NDMs falsamente positivas para OXA-48. Por ello, aunque de forma global las 2 técnicas fenotípicas mostraron resultados similares, la baja especificidad de los DI para la detección de OXA-48 deja a esta técnica en clara desventaja, como se ha demostrado en otros estudios [10].

Estos resultados de baja especificidad con los DI y el tiempo de detección más prolongado nos llevaron a utilizar el TIC (modificado con calor) como técnica de elección para el cribado de carbapenemasas, dejando a las técnicas genotípicas, las cuales proporcionaron el mejor rendimiento, como demuestran los datos de BF [11], únicamente para confirmación de cepas dudosas con antibiograma compatible.

Por otro lado, hasta el momento, en nuestro hospital no se han detectado carbapenemasas de tipo IMP ni KPC en Enterobacterales, por lo que no ha sido posible su evaluación, lo que supondría una de las limitaciones de nuestro estudio. Además, el tamaño muestral de otro tipo de MBL no NDM, fue muy pequeño y poco valorable. Por todo ello, es necesario continuar evaluando estas técnicas en todos los tipos de carbapenemasas, y especialmente el nuevo Kit Coris Resist-5 O.K.N.V.I. que incorpora la detección de IMP, empleando además un buffer modificado para mejorar la visualización de las bandas de MBL.

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CONFLICTO DE INTERÉS

Los autores declaran no tener ningún conflicto de interés.

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Brief report

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Prevalence of mutations associated with macrolide and fluoroquinolone resistance in *Neisseria gonorrhoeae* with Allplex™ NG&DR Assay (Seegene®) in a tertiary hospital from Madrid, Spain

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ABSTRACT

Background. The prevalence of drug-resistant *Neisseria gonorrhoeae* (NG) infections is increasing. Studies report the prevalence of NG strains presenting A2059G/C2611T (rRNA 23S) and S91F (*parC*) mutations conferring resistance to azithromycin and ciprofloxacin.

Material and methods. We conducted a prospective cohort study evaluating first void-urine urines, rectal, and oropharyngeal swabs collected from a cohort of patients in a tertiary hospital in Madrid between October 2022 and January 2023. Samples were screened by Allplex™ 7-STI Essential Assay (Seegene®). Drug resistances were performed by Allplex™ NG&DR Assay (Seegene®).

Results. A total of 1,415 patients were included, of which 112 had a positive sample for NG infection. One patient had a C2611T mutation (0.9%) and neither patient showed A2059G mutation. We found 67 (59.8%) S91F-positive patients. Forty-four patients (39.3%) not had any mutations.

Conclusions. We report a low-prevalence of mutations A2059G/C2611T to macrolides and a high-prevalence to S91F in NG infections. Molecular methods for the detection of NG resistance could be useful in direct non-culturable samples.

Keywords: *Neisseria gonorrhoeae*; azithromycin; ciprofloxacin; antimicrobial resistance; mutations

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Prevalencia de mutaciones asociadas a resistencia a macrólidos y fluoroquinolonas en *Neisseria gonorrhoeae* con el kit Allplex™ NG&DR Assay (Seegene®) en un hospital terciario de la Comunidad de Madrid, España

RESUMEN

Introducción. La infección por *Neisseria gonorrhoeae* (NG) resistente está aumentando. Se ha descrito la prevalencia de cepas de NG con mutaciones A2059G/C2611T (rRNA 23S) y S91F (*parC*) que confieren resistencia a azitromicina y ciprofloxacino.

Material y métodos. Realizamos un estudio prospectivo evaluando orinas de primera micción, hisopos anales y faríngeos recogidos de una cohorte de pacientes en un hospital terciario de Madrid entre octubre de 2022 y enero de 2023. El cribado de las muestras se realizó mediante Allplex™ 7-STI Essential Assay (Seegene®). Las resistencias a macrólidos y fluoroquinolonas se realizaron mediante Allplex™ NG&DR Assay (Seegene®).

Resultados. Se incluyeron 1.415 pacientes, de los cuales 112 fueron positivos para NG. Un paciente presentaba una mutación C2611T (0,9%) y en ningún paciente se detectó A2059G. Encontramos 67 pacientes (59,8%) positivos para S91F. Cuarenta y cuatro pacientes (39,3%) no presentaban mutaciones.

Conclusiones. Reportamos una baja prevalencia de mutaciones A2059G/C2611T a macrólidos y una alta prevalencia de S91F en NG. Los métodos moleculares para la detección de resistencias en NG podrían ser útiles en muestras directas no cultivables.

Palabras clave: *Neisseria gonorrhoeae*; azitromicina; ciprofloxacino; resistencia antimicrobiana; mutaciones

INTRODUCTION

Antimicrobial resistance in *Neisseria gonorrhoeae* (NG) is increasing worldwide. Mechanisms of NG resistance to macrolides include chromosomal mutations, genes encoding rRNA methyltransferases, and overexpression of efflux pumps [1]. Resistance to fluoroquinolones is mainly due to the presence of mutations in the *gyrA* or *parC* genes [2]. The first-line treatment for NG infections is third-generation cephalosporins, such as intramuscular ceftriaxone or oral cefixime. Macrolides (azithromycin) are a second-line treatment that should not be used in monotherapy. Treatment with fluoroquinolones (ciprofloxacin) may be an option in allergic or intolerant patients to third-generation cephalosporins, provided that a *gyrA* mutation is not detected following the sexually transmitted infections guidelines [3,4]. The resistance rates to macrolides and fluoroquinolones are well known for *Mycoplasma genitalium* infections due to the large supply of commercially available assays [5-7]. However, new commercial kits are emerging for the detection of mutations associated with therapeutic failure of these second-line treatments using nucleic acid amplification tests (NAAT) for NG infection. [8]. We have researched the epidemiology and prevalence of macrolide and fluoroquinolone resistances in patients with *N. gonorrhoeae* sexually transmitted infection collected at Hospital Universitario La Paz (HULP), a tertiary hospital from Madrid, Spain.

MATERIAL AND METHODS

In a prospective observational cohort study design, we collected the demographic, clinical, and analytical data of patients with NG infection (as confirmed by RT-PCR) from the hospital database and laboratory informatics systems from October 2022 to January 2023. Only one NG sample by patient was included in the study. In addition, sexually transmitted coinfections and serological data were collected from patients during the NG infection episode.

Genitourinary samples were screened for NG by real-time PCR Allplex™ 7 STI Essential Assay (Seegene®, Seoul, South Korea), which includes *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Mycoplasma genitalium*, among others STI pathogens. Positive samples for NG were analyzed with the new kit Allplex™ NG & DR Assay (Seegene®) to study mutations associated to macrolides and fluoroquinolones resistance. This is a new commercial kit authorized for in vitro diagnostic use (IVD). 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 was detected by the S91F (*gyrA*) mutation including in the assay. The RT-PCR was performed in combination with automated DNA extraction and PCR setup using a Microlab STARlet Liquid Handling robot (Hamilton®), according to the manufacturers' instructions. Genitourinary samples were amplified by CFX96™ Touch Real-Time PCR Detection System thermal cycler (BioRad®, Hercules, California). Seroprevalence data about patients were collected for HIV (Anti-HIV/Ag-p24), syphilis (IgG), HBV (Anti-HBc IgG), and HCV (IgG). Serological analysis was performed by Atellica (Siemens Healthcare Diagnostics®, Germany).

RESULTS

A total of 1,415 (765 males and 650 females) patients were screened for NG infection of which in 112 patients (8%) NG was detected. The proportion of males (n=101, 90.2%) with NG infection was higher than females. The median age of the patients was 29 years-old (IQR: 23-37). In the seroprevalence study, twenty-five out of 96 patients (26%) were positive for HIV, 32/98 (32.7%) had syphilis-positive, 10/84 (11.9%) were HBV-positive, and 5/96 (5.2%) had HCV-positive. Thirteen (11.6%) out of the 112 patients had no serological records at our center.

Specimens collected were mainly first void-urines (75 samples) following by rectal (26 samples), and oropharyngeal swabs (11 samples). Twenty-one out of 112 patients (18.8%) had some sexually transmitted coinfection during the study with *Chlamydia trachomatis* (n=20) or *Trichomonas vaginalis* (n=1) (Table 1).

In 44 patients were not detected any mutation associated

Table 1 **Distribution of mutations associated with macrolide and fluoroquinolone resistance by sample and sexually transmitted coinfections (STCs).**

Sample	Total	STCs (n)	NM (n)	%	Macrolide resistance (n)		%	Fluoroquinolone resistance (n)	%
					A2059G	C2611T		S91F	
First-void urine	75	15 (1CT, 1TV)	25	33.3%	0	1	1.33%	48	64%
Anal Swab	26	6 CT	13	50%	0	0	0%	13	50%
Oropharyngeal swab	11	0	5	45.4%	0	0	0%	6	54.6%
Total	112	21	44	39.3%	0	1	0.9%	67	59.8%

NM: Non-mutations detected, CT: *Chlamydia trachomatis*, TV: *Trichomonas vaginalis*

with macrolide or fluoroquinolone resistance. A single mutation C1126T (23S rRNA) associated with moderate-level macrolide resistance was only detected in one patient from first-void urine. Neither A2059G (23S rRNA) mutation associated with high-level macrolide resistance was detected. No macrolide resistance-associated mutations in *N. gonorrhoeae* were detected in 99.2% of the samples. However, in 67 strains of NG (59.8%) the S91F mutation associated with fluoroquinolone resistance in *gyrA* gene was detected.

DISCUSSION

We have reported the prevalence of mutations associated with macrolide and fluoroquinolone resistance in our population with *Neisseria gonorrhoeae* infection. Most of the patients were sexually active males with a positive serological status (HIV, syphilis, HBV, or HCV). The sexually transmitted coinfections were mainly by *C. trachomatis*.

The therapeutic use of azithromycin represents a useful therapeutic line always in combination with other drugs for NG infection. Sanchez-Busó *et al.* reported an overall prevalence in Europe of 8% of macrolide resistance [9]. In Spain, azithromycin sensitivity studies of NG have been reported by the gradient diffusion methods. The prevalence of azithromycin resistance contrasts between 2-12% [10–13]. However, no studies using NAAT methods have been described. The prevalence of mutations A2059G and C1126T associated with high/moderate-level macrolide resistance in our study population was low according with other reports [9,14]. However, there are other mechanisms of macrolide resistance that imply therapeutic failure of NG infections and are not detected by the assay, such as A2058G high macrolide resistance, or resistances associated with overexpressed of efflux system, among others [1,14]. Kandinov *et al.* reported an overexpression of efflux pumps by mutations in the MtrCDE genes causing more than 90% of azithromycin resistance.

We found a high prevalence of S91F mutation associated with failure to fluoroquinolones treatment in NG infection according with another report in Europe [9]. The highest prevalence of fluoroquinolone resistance was detected in urine due to maybe to the higher representation of gonococcal urethritis. According to this high prevalence, STI therapeutic guidelines recommend prior screening for mutations in the *gyrA* gene before treatment with fluoroquinolones [3]. In the same way, other mutations associated with fluoroquinolones resistance such us D95A, D95G, or D95N (*gyrA*) or D86N (*parC*) are not included in the Allplex assay although these mutations are less prevalent [9]. Secondly, the highest prevalence of fluoroquinolone resistance was found in pharyngeal samples. In addition, fluoroquinolones resistance was detected in the half of the rectal samples. However, the presence of commensal *Neisseria* species with resistance to fluoroquinolones in clinical samples (such as pharyngeal or rectal swabs) could lead to false-positive results for the S91F mutation. The culture would be necessary to select *N. gonorrhoeae* in this type of samples.

As a limitation of our study, no data were collected on the sexual practices of patients. Moreover, these detection of a little number of mutations could imply underdiagnoses of macrolide and fluoroquinolone resistance. Therefore, it would be necessary to evaluate the correlation between the detection of these resistances by NAAT and the MICs values obtained by standard resistance methods from EUCAST/CLSI breakpoints or next generation sequencing (NGS) in other studies.

In conclusion, the Allplex™ NG&DR Assay kit (Seegene®) has some limitations in clinical use due to the empirical use of third-generation cephalosporins as first-line treatments for NG infections and the possibility of detecting resistances from commensal species. However, the assay could be useful in cases where targeted therapy with fluoroquinolones (if no resistance mutations are detected) is established in patients who have not received empirical treatment. In addition, the useful in joint fluid for gonococcal arthritis diagnoses should be studied due to the use of fluoroquinolones in this clinical entity [15]. Moreover, the detection of macrolide or fluoroquinolone resistance-associated mutations in NG by NAAT methods could be useful in direct clinical samples such as first-void urine or when NG strains cannot be isolated due to lack of growth. Furthermore, mainly the assay could be useful epidemiologically to monitor the emergence of resistant NG without the need for positive culture or NGS studies.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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Letter to the Editor

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Identification of curved Gram-negative rods by MALDI-TOF mass spectrometer in a patient with Fournier´s gangrene. A bacteremia caused by *Desulfovibrio desulfuricans* and *Escherichia coli*

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Sir,

Desulfovibrio desulfuricans are obligate anaerobic gram-negative rods, curved, sulphate-reducing and commensals of the gut microbiota. *Desulfovibrio* genus comprises more than 60 species, however, only *D. desulfuricans, Desulfovibrio fairfieldensis, Desulfovibrio vulgaris, Desulfovibrio piger, Desulfovibrio legallii* and *Desulfovibrio intestinalis* have been clinically isolated up to now [1].

A 69-year-old patient with a history of untreated chronic obstructive pulmonary disease was found at home with deterioration of consciousness, respiratory failure and poor general condition. Physical examination showed signs of hemodynamic instability with blood pressure of 63/33 mmHg, oxygen saturation of 78%, poor perfusion, abdominal lividity, capillary refill > 2 seconds, sweaty. Furthermore, the patient presented extensive gangrene of the scrotal area, penile base and perianal region, crepitant on palpation and incarcerated left inguinal hernia. He was taken to the emergency department with a diagnosis of Fournier's gangrene, with the need for vasoactive drugs. Initial laboratory tests showed: hemoglobin 8.9 g/dL, 29750 leukocytes with 91.50% neutrophils, glucose 98 mg/dL, urea 229 mg/dL, GPT 139 U/L, creatinine 2.81 mg/dL, glomerular filtration rate 22 mL/min/1. 73 m2, creatine kinase 6362 U/L, C-reactive protein 329.46 mg/L, prothrombin index 41%, INR 1.9, activated partial thromboplastin time 38 seconds, fibrinogen 634 mg/dL. A blood culture sample was obtained, he underwent surgery with debridement (intraoperative sample was also obtained) and was admitted to the resuscitation department with 2 g/8 h of IV meropenem, 600 mg/8 h of IV clindamycin and 500 mg/24 h of IV daptomycin.

The blood culture was incubated in the BD BACTEC® system (Becton Dickinson, New Jersey, USA) and one of the aerobic vials (BD BACTEC™ Plus Aerobic/F Culture Vials) was positive at 14 h of incubation. Gram staining showed Gram-negative bacilli and it was subcultured on chocolate (incubated at 37 °C in 7% CO_2 atmosphere) and MacConkey (incubated at 37 °C in aerobiosis) agars. After 24 h, growth was identified as *Escherichia coli* by MALDI-TOF mass spectrometer (Bruker, Massachusetts, USA) with a score of 2, 33. One of the anaerobic vials (BD BACTEC™ Lytic/10 Anaerobic/F Culture Vials) was positive after 4 days of incubation, whose Gram staining revealed curved, short, spiral Gram-negative rods (Figure 1, right image). It was subcultured on chocolate and BD® Brucella Blood with Hemin and Vitamin K1 agars (incubated at 37°C in an anaerobic atmosphere) and after 72 h, small colonies 0.5-1 mm in diameter, round and shiny were observed on Brucella agar (Figure 1, left image) and identified as *D. desulfuricans* by MALDI-TOF MS (Bruker, Massachusetts, USA) with a score 2.2. The antibiotic susceptibility of *D. desulfuricans* was studied by MICs with antibiotic gradient strips or E-test® (Liofilchem, Teramo, Italy) on Brucella agar under anaerobic conditions. The strain was susceptible according to EUCAST 2020 breakpoints guidelines (Gram-negative anaerobes) to amoxicillin + clavulanic acid (MIC=0.12 mg/L), imipenem (MIC=0.25 mg/L), meropenem (MIC= 0.06 mg/L), clindamycin (MIC=0.5 mg/L), metronidazole (MIC=0.06 mg/L) and resistant to piperacillin/tazobactan (MIC 128 mg/L), although currently *D. desulfuricans* does not have cut-off breakpoints.

The intraoperative sample was inoculated on chocolate, CNA and TSA agars with 5% sheep blood (Becton Dickinson, New Jersey, USA), MacConkey, Brucella y BBE with Amikacin agars. Chocolate, TSA with 5% of sheep blood and CNA agars were incubated in microaerophlic conditions, MacConkey agar in aerobiosis, whereas Brucella and BBE with Amikacin agars in anaerobiosis. Gram staining showed no leucocytes and no microorganisms, nevertheless *E. coli* and *Bacteroides thetaiotaomicron* grew at 24 h in McConkey agar and at 48h in Brucella agar by MALDI-TOF MS, respectively. *D. desulfuricans* did not grew in these subcultures, but its presence cannot be ruled

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Figure 1 **Left figure: subculture of the positive anaerobic bottle in Brucella agar after 72-96 h of incubation in anaerobic conditions. Brightly and small colonies growing at the bottom of the agar were identified as *Desulfovibrio desulfuricans* with MALDI-TOF MS.**
Right figure: gram staining of the anaerobic bottle showed curved Gram-negative rods (scale x1000).

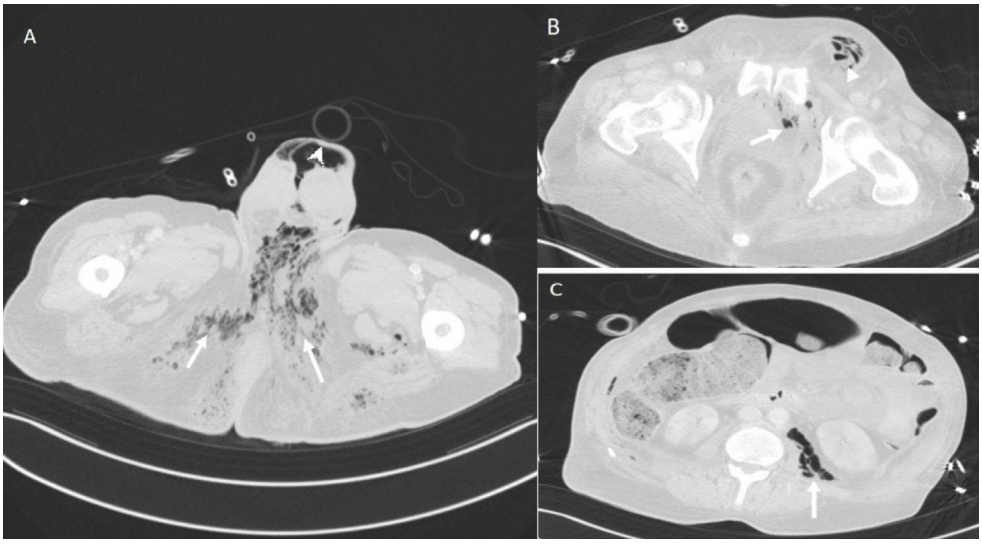

Figure 2 **2A: abdominopelvic CT with lung-window showing a large amount of gas dissecting the fatty and muscular planes of the gluteal and perineal region (arrows) with extension to the scrotum (arrowhead). In figure 2B, we observe ascension towards the obturator internus muscle (arrow) and inguinal canal (arrowhead). In figure 2C, we observe how the emphysema extends into the retroperitoneal space, dissecting mainly the left posterior pararenal fascia (arrow).**

out given its fastidious growth (the subcultures were discarded after the identification of these two microorganisms).

A thoracic-abdominal-pelvic CT scan showed findings consistent with Fournier´s gangrene, as well as neoplastic disease in the rectum with possible fistulization towards the ischiorectal collection and liver metastases (Figure 2). Several hours after surgery, the patient presented abruptly increased hemodynamic instability with multiorgan failure. Subsequently, he went into cardiorespiratory arrest without improving after cardiopulmonary resuscitation maneuvers and finally died.

D. desulfuricans is characterized by the presence of a pigment, desulfoviridin (with blue-green fluorescence at acid pH and red fluorescence at alkaline pH) [2]. *D. desulfurincans* has rarely been described in human infections; however, it has been previously isolated causing bacteremia [3], liver abscesses [4] or septic arthritis [5]. Immunosuppression (malignancy or

diabetes), gastrointestinal disease, history of trauma or previous surgery are known risk factors for these infections [4,5]. Our patient did not have medical history of interest, but the CT-scan performed during hospitalization showed possible premalignancy

The identification of fastidious microorganisms such as *D. desulfuricans* has been hindered in the past years by the limitations of biochemical methods or by the limited availability of molecular identification technics such as 16S rRNA gene sequencing in most laboratories. However, in recent years, this has changed with the introduction of the MALDI-TOF mass spectrometer into the routine of many laboratories. It is an accurate, inexpensive and accessible tool relative to molecular methods, which has shortened the time to identify these bacteria [6].

Optimal treatment of *D. desulfuricans* infections is still unclear; however, it should be taken into account that this anaerobe may produces beta-lactamases [7]. Metronidazole, clindamycin, chloramphenicol or carbapenems can be used, whereas amoxicillin/clavulanic usually shows good in-vitro activity and most strains present high MICs to piperacillin/tazobactam [8] (as in our case). Given the general susceptibility of the strains studied so far, piperacillin/tazobactam and cephalosporins should be avoided as antibiotic treatment. However, given the good evolution in most cases [1,3-6,8], combined treatments do not seem necessary (except in infections associated with other gram-negative or gram-positive microorganisms, as well as in the empirical treatment of severe intra-abdominal infections). Despite correct antibiotic treatment, control of the focus is mandatory in most infections like the presented case [9].

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Letter to the Editor

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Malignant syphilis in HIV negative patient treated with ibrutinib

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Sir,

Ibrutinib is a drug that irreversibly inhibits *Bruton Tyrosine Kinase* (BTK) - an enzyme involved in the development, activation, function, and survival of B-lymphocytes [1]. It is therefore a useful therapeutic option in neoplasms of this cell lineage (i.e. chronic lymphocytic leukaemia, Waldeström's macroglobulinaemia, mantle lymphoma and marginal zone lymphoma). The drug is easy to administer (orally), the response is fast and long-lasting, and it is generally well tolerated by the patient. However, several types of side effects such as haemorrhagic diathesis, atrial fibrillation, skin lesions, diarrhoea and opportunistic infections have been reported [2,3]. The main opportunistic infections described in patients treated with ibrutinib are classical bacterial (mainly capsular), fungal (*Aspergillus* spp. and *Pneumocystis jirovecii*) and viral (*Herpesvirus* family) infections [4-7]. However, the incidence, severity and type of microorganism are influenced by other factors such as the type of haematological malignancy, previous use of other drugs or concomitant use of immunosuppressive medication [4,5,8,9]. In this paper we report the association of ibrutinib treatment with malignant syphilis, a rare and severe manifestation of sexually transmitted infection.

A 51-year-old Caucasian man with a history of primary hypogonadism under replacement therapy and unprotected sexual relations with multiple partners. He was diagnosed with Waldenström's macroglobulinemia, receiving a first line of treatment with 6 cycles of cyclophosphamide, dexamethasone and rituximab, with poor clinical response. Subsequently, a second line of 6 cycles of bortezomib, dexamethasone and rituximab were administered, despite of that, a sudden increase in the monoclonal component was observed so it was finally decided to start treatment with ibrutinib, with an excellent initial response.

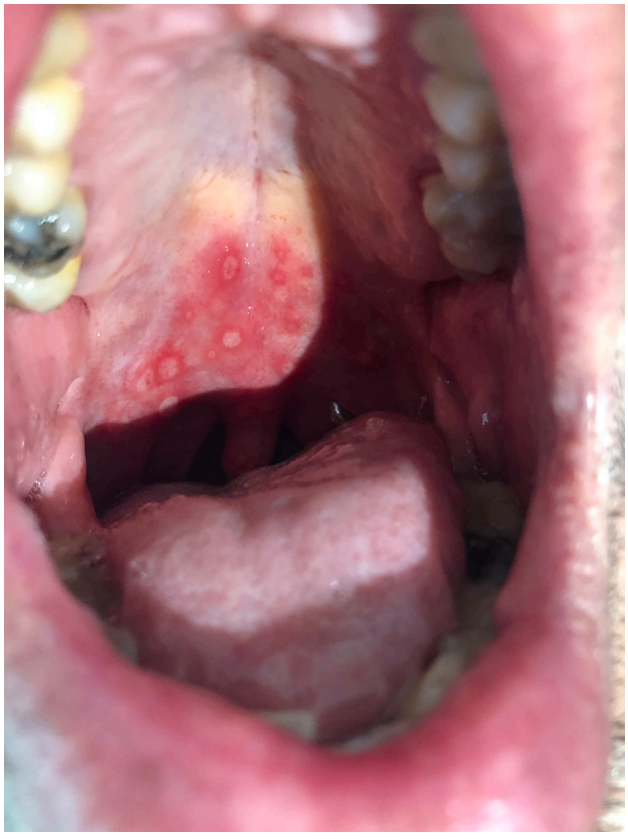

Figure 1 | **Oral Herpes simplex virus type 1 infection**

Five months after starting treatment the patient was referred to the outpatient infectious diseases unit relating a two-months multiple painful ulcerative lesions on the soft palate, without neither genital nor other areas affected. He was afebrile. Physical examination revealed multiple erythematous

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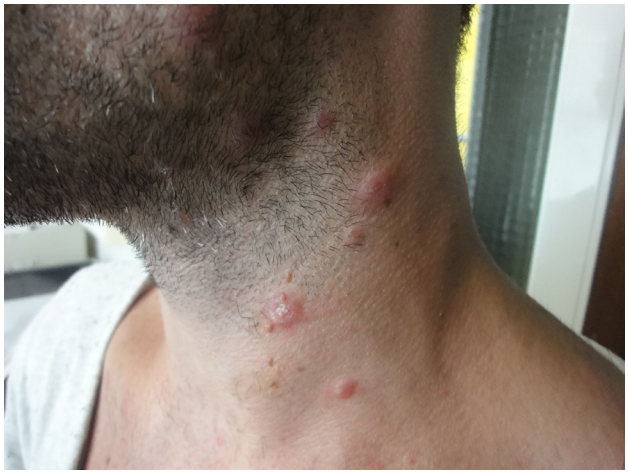

Figure 2 | **Malignant syphilis**

non-exudative aphthae on the soft palate without pillars or uvula involvement (Figure 1). One of the lesions was cultured, *Herpes simplex* virus type 1 was isolated and treated with valacyclovir with a good outcome. It should be noted that the patient had previous positive herpes simplex virus serology. Two months later, he returned to the clinic with a two-week course of fever, myalgia and the appearance of disseminated lesions (face, calotte, neck, chest, limbs, genitals and palms of the hands). These lesions were in different stages of evolution, some of them crusted (Figure 2). Direct microbiological examination of the lesions did not report bacteria, fungi or viruses. Serology showed RPR titres of 1:64 and HIV serology was repeatedly negative. With the diagnosis of malignant syphilis, treatment with penicillin was started and the lesions solved completely. One month later, he came for a check-up reporting two-week duration yellowish diarrhoea with non-pathological products, six stools per day approximately, without fever. The coproparasitic study showed *Giardia intestinalis* cysts and treatment with tinidazole was started, with resolution of the diarrhoea. HIV serology remained negative. Two years after the last event, the patient did not report new infectious complications.

Ibrutinib is a covalent inhibitor of several tyrosine kinase-active enzymes of the Tec (*transient erythroblastopenia of childhood*) family [3]. The effect on B-lymphocyte-derived neoplasms derives mainly from action on Bruton's tyrosine kinase (BTK) acting in the B-cell receptor (BCR) signalling pathway. It is therefore logical that the use of ibrutinib is associated with infections by capsulated bacteria and enteroviruses, such as in X-linked congenital agammaglobulinemia [10]. However, ibrutinib, unlike other BTK inhibitors (covalent or not), also exerts this effect on other Tec family enzymes such as BMX (*bone marrow tyrosine kinase on chromosome X)*, ITK (*interleukin 2-inducible T cell kinase*), RLK (*resting lymphocyte kinase*) and TEC (*tyrosine kinase expressed in hepato-cellular carcinoma*). T lymphocytes express three of these kinases (ITK, TEC and RLK), so complication of ibrutinib treatment with intracellular infections (especially fungal and viral) is possible [11].

Two factors are involved in the pathogenesis of any infectious disease: the causative agent and the host's defense mechanisms. In the patient described in this study, three infectious diseases were observed in a short period of time. Initially, a reactivation of herpes simplex type 1, with more aggressive features than the forms appearing in immunocompetent subjects. Afterwards, he developed a clinical and biological condition corresponding to malignant syphilis. This syndrome is characterised by the appearance of crusty ulcerated skin lesions accompanied by systemic manifestations such as fever, headache, myalgia, lymphadenopathy or visceral involvement [12,13]. Malignant syphilis is rare in immunocompetent individuals and has been described especially immunosuppressed patients (mainly in HIV co-infected and occasionally in association with immunosuppressive treatment [12,14]. Furthermore, the patient suffered from a *Giardia intestinalis* enteritis, probably related to risky sexual practices [15].

The above data suggest on the one hand that, although the association with skin lesions and diarrhea are well described nonspecific manifestations in patients receiving ibrutinib, it seems justified to look for associated infectious factors that can be specifically treated before attributing them to drug toxicity. On the other hand, we should really consider STI prevention in patients receiving ibrutinib.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Original

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Wound infection caused by *Pasteurella canis* and *Neisseria animaloris* after a dog bite

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Sir,

A 24-year-old patient attended the emergency department after a dog bite on her right hand. On examination, she presented a deep wound in the index finger of the right hand, without other associated complications. Anti-tetanus toxoid was prescribed, the wound was cleaned and desinfected without suturing, and she was discharged with 500 mg/8 h of oral amoxicillin/clavulanic acid completing 7 days of treatment. After 3 days, the patient came again to the emergency department due to worsening of her condition On examination she presented edema, erythema, and increased temperature in the second finger of the right hand, with associated collection. Blood tests showed 15000 leukocytes/µL with 11200 neutrophils. Surgical debridement was conducted, opening of the tendon synovial sheath and opening of the "A1 pulley", and two samples were obtained through needle aspiration for cultures. Antibiotic treatment was started with clindamycin and amoxicillin/clavulanic acid (600 mg/24 h and 1200 mg/8 h).

The samples were inoculated on chocolate agar, Columbia CNA agar and Tryptic Soy Agar (TSA) with 5% sheep blood (Becton Dickinson, New Jersey, USA), MacConkey agar, Brucella agar with hemin and vitamin K1 and BBE with Amikacin agar. Chocolate, TSA with 5% of sheep blood and CNA agars were incubated under aerobic conditions with 5% of CO_2 at 36±1ºC, MacConkey agar under aerobic conditions at 36±1ºC aerobiosis, whereas Brucella and BBE with Amikacin agars under anaerobic conditions at 36±1ºC. Gram staining showed Gram-negative bacilli and Gram-negative cocci, growing white-greyish colonies (Figure 2A) and scarce white-yellowish colonies (Figure 2B) after 48 h of incubation in TSA with 5% of sheep blood. The white colonies were identified as *Pasteurella* spp. using the API^R 20E strips (Biomerieux, Marcy-l'Étoile, France), while the yellowish colonies (Figure 2B) were identified as *Neisseria* spp. using the API^R NH strips, being this considered as a contaminant pending confirmation of the species. The susceptibility of *P. canis* was studied by MIC Test Strips^R (Liofilchem, Teramo, Italy) in BD^R Mueller Hinton Fastidious agar under aerobic conditions with 5% of CO_2 at 36±1ºC, and the interpretation was conducted according to the v13.0 European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [1]. *P. canis* was susceptible to penicillin (MIC = 0.38 mg/L), amoxicillin/clavulanic acid (MIC = 0, 38 mg/L), cefotaxime (MIC = 0.02 mg/L), doxycycline (MIC = 0.5 mg/L), ciprofloxacin (MIC = 0.06 mg/L) and trimethoprim/sulfamethoxazole (MIC = 0.125 mg/L). After two days, the wound was evaluated again, presenting somewhat necrotic edges with good appearance, without suppuration or erythema (Figure 1B). Antibiotics were changed to ciprofloxacin (400 mg/12 g IV) due to the onset of diarrhea, completing 10 days of treatment. She was discharged with good wound evolution and on oral ciprofloxacin (500 mg/12 h).

Species identification was conducted by 16S rRNA gene sequencing, obtaining two sequences of 450 and 473 bp were obtained, which were analyzed by BLAST^R and identified as *Pasteurella canis* and *Neisseria animaloris* with an identification rate of 98.89% and 99.37%, respectively. Both sequences were registered in GenBank^R with accession numbers "OP326753" for *P. canis* and "OP326754" for *N. animaloris*. Given the good evolution and non-viability of the strain, no additional testing was performed for *N. animaloris*.

Infections following animal bites or scratches in humans are usually polymicrobial, reflecting the oral flora of the animal producing the injury through bites or scratches [2]. Contact with the saliva of colonized or infected animals is also a possible route of transmission of zoonotic infections. In fact some infections caused by *Pasteurella spp.* or *Capnocytophaga canimorsus* (mouth commensals of dogs or cats) may not be preceded by bites or scratches [3,4].

Skin and soft tissue infections are most frequently caused

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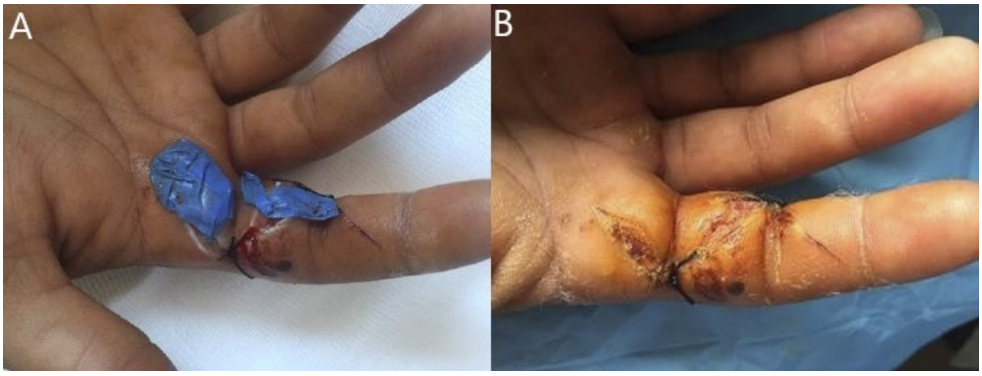

Figure 1 A: Surgical debridement of wound following dog bite due to complication with cellulitis and purulent collection.
B: Wound improvement with decreased cellulitis and erythema and absence of pus.

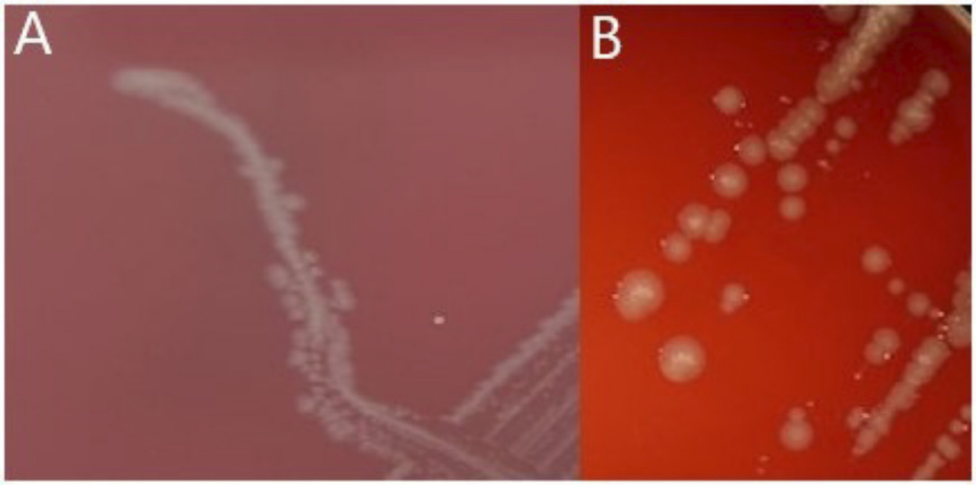

Figure 2 2A: growth of white-greyish colonies in TSA with 5% of sheep blood were firstly identified as *Pasteurella* spp. and then, species identification confirmed it as *P. canis*.
2B: growth of white-yellowish colonies in TSA with 5% of sheep blood were firstly identified as *Neisseria* spp. and then, species identification confirmed it as *N. animaloris* (we did not store an image the type of growth of *N. animaloris*, image belongs to Moa Skarin, Lise-Lotte Fernström & Ingrid Hansson).

by bacteria of the genus *Pasteurella*, with *Pasteurella multocida* being the most prevalent species. The most severe infections usually occur in patients who are immunocompromised, with comorbidities, or at extreme ages of life [3,5]. *P. canis* has been also reported causing from mild to severe infections such as skin and soft tissue infections to bacteremia or osteomyelitis [6,7]. In a retrospective study, *P. multocida* (48%) and *P. canis* (11%) were the main species found [7].

On the other hand, *N. animaloris* are Gram-negative facultative anaerobic cocci with arginine-dehydrolase activity, which reduce nitrites to gas and belonging to CDC group EF-4a as Gram-negative microorganisms recovered from human wound after dog or cat bites. [8]. It has been rarely reported causing both monomicrobial and polymicrobial infections with good response to treatment with beta-lactams or quinolones [9,10].

In the management of these infections, it is important to clean the wound with soap and water. The use of postexposure

antibiotic prophylaxis is controversial, although hand injuries seem to benefit from it, significantly decreasing infection rates. Beta-lactams, tetracyclines, or the combination of quinolones with clindamycin are often used as antibiotic prophylaxis [11]. In case of extreme pain, exposure of underlying muscle or bone, signs of superinfection, if the dog's rabies vaccination status or the patient's tetanus vaccination status is unknown, appropriate evaluation and treatment is important.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Carta al Director

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Infección de prótesis articular por *Clostridioides difficile* y revisión de la literatura

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Estimado Editor: La infección por *Clostridioides difficile*, bacilo anaerobio grampositivo, productor de toxinas y formador de esporas, se caracteriza por causar infecciones del tracto intestinal, siendo la colitis pseudomembranosa la presentación más frecuente [1]. El principal factor de riesgo es la exposición a antibióticos, aunque la edad avanzada, hospitalización o inmunosupresión [2] serían otros factores.

C. difficile presenta capacidad de producir exotoxinas, constituyendo su principal factor de virulencia. La toxina A (TcdA) es la responsable de unirse al epitelio intestinal y la toxina B (TcdB), del daño epitelial (efecto citotóxico) [1]. La afectación extraintestinal por *C. difficile* es poco frecuente, aunque se han descrito casos de infecciones de piel y partes blandas [3]. Sin embargo, la infección de prótesis articular (IPA) es una manifestación extremadamente rara. A continuación, se presenta el caso de una paciente con IPA precoz de cadera por *C. difficile*.

Mujer de 89 años, institucionalizada en centro sociosanitario, con sarcoidosis pulmonar y deterioro cognitivo leve, índice de Charlson 7 puntos. Ingresa por colecistitis aguda litiásica tratada con amoxicilina-clavulánico. Tras 16 días, presenta cuadro diarreico con deposiciones verduzcas, se realiza estudio de *C. difficile* en heces, siendo la inmunocromatografía (GDH+Toxinas A/B) negativa, pero en PCR (AllplexTMGastrointestinal Assay) se detectan los genes que codifican para las toxinas A/B de *C. difficile*. Se pauta vancomicina oral 7 días y es dada de alta.

Dos meses más tarde, tras caída casual, presenta fractura subcapital de cadera izquierda y es intervenida mediante artroplastia parcial. Durante ingreso, desarrolla nuevamente síndrome diarreico sugestivo de colitis y se inicia antibioterapia empírica (se desconoce si se realizó detección de *C. difficile* y la antibioterapia al realizarse la intervención en centro externo), presentando buena evolución clínica.

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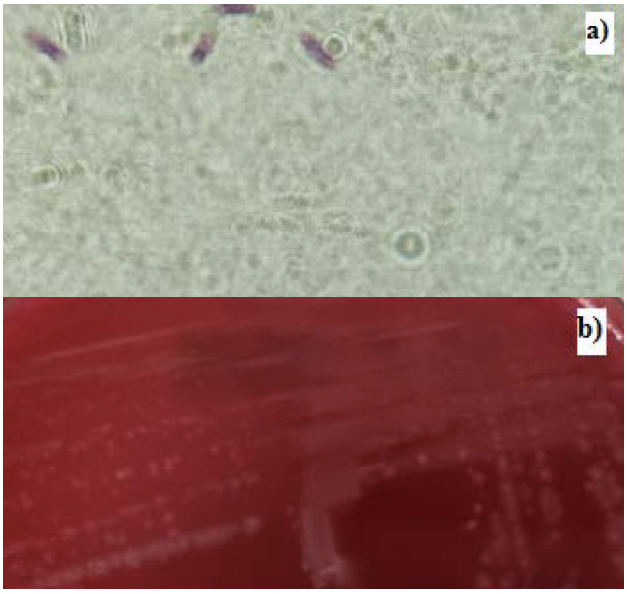

Figura 1 **a) Bacilo grampositivo en la muestra de líquido articular. b) Colonia *C. difficile*.**

Veinte días más tarde, acude a urgencias de nuestro centro por taquicardia, hipotensión y disnea, con inflamación local a nivel de herida quirúrgica de cadera, sin fiebre. En la exploración física, se identifica eritema circunscrito en zona de herida quirúrgica con aumento de temperatura y empastamiento local. Presenta dolor con la movilización en flexión y rotación interna. En analítica de sangre destaca PCR 11,6 mg/dL (0-0,5), con función renal, coagulación y plaquetas en rango, leucocitosis 25,80x10^9/L (4,5-10) con neutrofilia 81,2% y procalcitonina 4,18 ng/mL (<0,5 ng/mL). Ante la sospecha clínica de IPA se ingresa para completar estudio y se inicia tratamiento empírico con ceftriaxona. Se realiza resonancia de cadera que objetiva extensas colecciones glúteas y en tejido celular subcutáneo con

Tabla 1 **Comparativa de casos.**

	Caso 1 [5]	Caso 2 [6]	Caso 3 [7]	Caso 4 [8]	Caso 5 [9]	Caso 6 [10]	Caso 7 [11]	Caso 8 [12]	Nuestro caso
País	Inglaterra	Francia	Australia	América	América	Bélgica	España	China	España
Año	1994	1995	1999	2013	2013	2014	2021	2021	2022
Edad	31	16 años	83 años	61 años	47 años	61 años	79 años	75 años	89 años
Sexo	Mujer	Varón	Mujer	Mujer	Mujer	Varón	Varón	Mujer	Mujer
Comorbilidades	Anemia de células falciformes.Necrosis avascular bilateral de cadera	Osteosarcoma de fémur, radioterapia y quimioterapia	Neumonía nosocomial	Hipotiroidismo, asma	Hipotiroidismo, hepatopatía alcóholica, consumo marihuana	Diabetes, VIH, infección por CMV	Adenocarcinoma rectal, colostomía	Desconocido	Sarcoidosis pulmonar, insuficiencia cardíaca, deterioro cognitivo
Lugar de infección	Cadera	Rodilla	Cadera	Rodilla	Hombro	Cadera	Rodilla	Cadera	Cadera
Tipo de infección	Tardía (años)	Tardía (16 meses)	Tardía (12 meses)	Precoz (3 meses)	Precoz (3 meses)	Precoz (1 semana)	Tardía (10 años)	Tardía (24 meses)	Precoz (20 días)
Tratamiento quirúrgico	Desconocido	Artrotomía con drenaje y extracción de implante	Revisión de la cadera y eliminación de implante	Eliminación de implante	Desbridamiento y eliminación del equipo	Desbridamiento y retención	Recambio en dos tiempos	Desbridamiento y recambio de artroplastia en dos tiempos	Recambio de prótesis en dos tiempos.
Tratamiento antibiótico	Metronidazol intravenoso	Amoxicillina Ornidazol Rifampicina Lincomicina Penicillina G	Metronidazol	Piperacilina- Tazobactam Metronidazol	Vancomicina Metronidazol	Vancomicina Metronidazol	Sellado vancomicina y gentamicina en 1ª tiempo con metronidazol oral. Teicoplanina intravenosa y rifampicina oral, con sellado de vancomicina.	Vancomicina Metronidazol	Vancomicina
Resultado	Éxitus	Amputación	Satisfactoria	Amputación	Desconocido	Satisfactoria	Satisfactoria	Satisfactoria	Éxitus

realce periférico e inflamación de tejidos blandos adyacentes. Presenta deposiciones verdosas y con moco, pero no se obtienen muestras para estudio microbiológico. Los hemocultivos son negativos. Ante estos hallazgos, se decide intervención quirúrgica en dos tiempos, con retirada de prótesis y colocación de espaciador. Se recogen muestras en quirófano para estudio microbiológico y se amplía cobertura antibiótica con daptomicina dada persistencia de fiebre. En la tinción de Gram de las muestras quirúrgicas se observan bacilos Gram positivos (Figura 1A) y se aísla *C. difficile* y *Staphyloccocus epidermidis* en cultivos de líquido articular, tejido celular subcutáneo (2 muestras), cemento, biopsia de glúteo y biopsia de cápsula, cumpliendo criterios microbiológicos de IPA. La identificación se realiza mediante espectrometría de masas (MALDI-TOF MS) y el estudio de sensibilidad mediante microdilución en caldo (VITEK® 2) y tiras de E-test. *C. difficile* con CMI: 0,38mg/L a daptomicina y sensible a vancomicina (CMI: 0,25mg/L); *S. epidermidis* sensible a daptomicina (CMI: 0,5mg/L) y vancomicina (CMI: 1 mg/L). Se realiza PCR (GenomEra®) de la colonia de *C. difficile* (Figura 1B) siendo positiva para ambas toxinas. Se modifica antibioterapia a vancomicina 1g/12h intravenosa, ajustada posteriormente a función renal. La paciente presenta mala evolución clínica a pesar del tratamiento, falleciendo a los pocos días de la intervención.

En nuestro conocimiento, tan solo se han descrito 8 casos en la literatura de IPA por *C. difficile* (Tabla 1). De los casos presentes en la literatura, tan solo tres de ellos se corresponden con IPA precoz como nuestra paciente, siendo el primero descrito en España. Gran parte de las infecciones de prótesis por bacterias anaerobias publicadas hasta el momento se deben a la diseminación hematógena por translocación bacteriana intestinal [4]. En este caso, teniendo en cuenta una posible colitis pseudomembranosa intercurrente en el momento de la colocación de la prótesis y la posibilidad de que la paciente fuese portadora de *C. difficile*, dicha diseminación hematógena sería la vía de transmisión más probable.

En la actualidad, no existen guías clínicas ni publicaciones que hayan descrito el tratamiento adecuado para este tipo de infección extraintestinal, sin embargo vancomicina intravenosa, metronidazol y los betalactámicos son las opciones terapéuticas utilizadas con más frecuencia.

En conclusión, aunque la IPA por *C. difficile* es extremadamente rara, en pacientes que presentan colonización o infecciones recurrentes por este microorganismo, deberíamos de incluirlo en el diagnóstico diferencial, siendo fundamental la recogida de muestras microbiológicas en condiciones adecuadas de transporte y conservación para la recuperación de anaerobios que ayuden a dicho diagnóstico.

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CONFLICTO DE INTERESES

Los autores no presentan ningún conflicto de intereses.

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Carta al Director

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Infección cutánea por *Bacillus licheniformis*

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Estimador Editor; *Bacillus licheniformis* es un bacilo anaerobio facultativo, grampositivo, formador de esporas en aerobiosis y con interés biotecnológico; es estable en condiciones atmosféricas adversas como calor y humedad.

Presenta resistencia a la secreción gástrica usándose en ocasiones como modulador de la microbiota intestinal; sin embargo, algunos probióticos que contienen *Bacillus* spp. se consideran inseguros por la producción de toxinas y el riesgo de transferir genes de resistencia a los antibióticos [1]. Cabe destacar que los estudios clínicos sobre el microbioma utilizando cepas probióticas de *Bacillus* spp. son limitados [1].

Las cepas *de Bacillus* spp. están muy extendidas en la naturaleza [1] y sus esporas permanecen viables durante años.

B. licheniformis produce un polímero de glutamato, que participa en la formación de una biopelícula [2], lo que refuerza su poder contaminante incluso en la industria alimentaria [3]. Igualmente, a *B. licheniformis* se le atribuye motilidad que facilita la invasión de barreras celulares humanas y no humanas [4].

Se reconoce cada vez más *B. licheniformis* como un patógeno humano capaz de causar bacteriemia, incluso persistente, por la posibilidad de permanencia en los tejidos de endosporas latentes que germinan periódicamente [5]. Existen contribuciones como la de Yuste y colaboradores quienes reportaron un caso de un absceso cutáneo por una espina vegetal en una niña inmunocompetente [2], y también Ameur et al. [6] publicaron el cuadro de una mujer con infección cutánea *por B. licheniformis* que introdujo una astilla de mimbre [7]. En inmunocompetentes puede existir inoculación directa en catéteres venosos centrales y válvulas protésicas [2]. Chuan Zhong et al. describieron una bacteriemia causada por la inyección accidental de *B. licheniformis* en catéter venoso central [7]. Se ha aislado también en casos de peritonitis, intoxicación alimentaria, infecciones oculares [8,9] y sinusitis maxilar [10].

Describimos el caso de un varón de 62 años, sin antecedentes personales de interés, derivado desde Atención Primaria a la consulta de Dermatología por presentar un nódulo indurado, eritematovioláceo y abscesificado con exudado purulento en la región interna del muslo izquierdo de un mes de evolución, tratado con antibioticoterapia oral empírica (amoxicilina-clavulánico) y tratamiento tópico (curas con mupirocina, betametasona/gentamicina), sin mejoría clínica. Como antecedente epidemiológico de importancia el paciente habitualmente trabajaba en un huerto. Atendido por Dermatología, se suspendió antibioticoterapia y se realizó previa limpieza de la piel con solución fisiológica estéril una toma de muestra de exudado cutáneo para cultivo bacteriano y de hongos, utilizando escobillón flocado con medio de transporte tipo Amies.

La siembra se realizó en el Servicio de Microbiología en medios de cultivo agar sangre, agar chocolate, agar brucella y caldo tioglicolato con resazurina en condiciones de aerobiosis y anaerobiosis; y medio de Sabouraud. Se aíslan, a las 48 h de incubación, en placa de agar sangre colonias de igual morfotipo, rizoides y betahemolíticas. En tinción de Gram se observan bacilos grampositivos. Se procede a la identificación del microorganismo mediante MALDI-TOF VITEK®MS: *Bacillus licheniformis* (score 99,9%).

La sensibilidad antibiótica se determinó en medio de cultivo MHF Biomerieux®, McFarland 0.5, interpretado según criterios EUCAST 2022, mediante técnica de difusión en gradiente utilizando tiras de E-test Biomerieux® e incubación posterior en atmósfera aerobia a 35 ± 1ºC, 18 ± 2 horas. El antibiograma mostró sensibilidad a imipenem (CMI 0,094 mg/L), ciprofloxacino (I) (CMI 0,064 mg/L), vancomicina (CMI 1 mg/L), linezolid (CMI 0,25 mg/L); asimismo presentó resistencia a clindamicina (CMI 16 mg/L) y a eritromicina (CMI 26 mg/L). El cultivo de anaerobios y hongos resultó negativo.

Se pautó tratamiento antibiótico con ciprofloxacino vía oral a altas dosis 750 mg cada 12 horas durante 1 semana,

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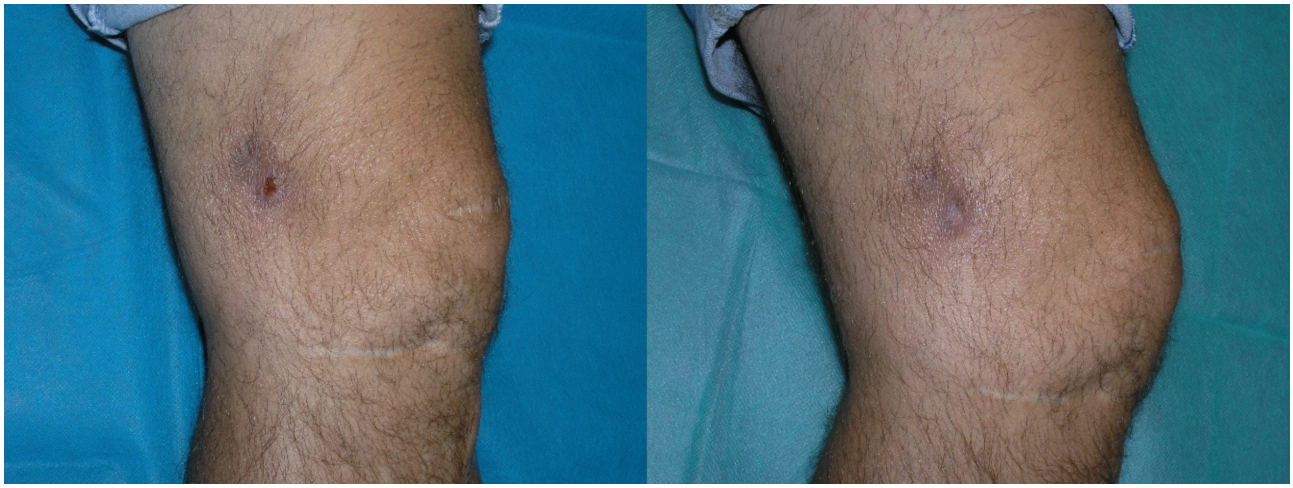

Figura 1 | **Lesión antes (imagen izquierda) y después (imagen derecha) del tratamiento con ciprofloxacino.**

con mejoría clínica evidente y posterior curación de la lesión; la evolución ha sido igualmente favorable en la revisión a los 3 meses post curación con cicatriz hipopigmentada y plana (Figura 1). En vista de seguimiento satisfactorio no se realizaron pruebas diagnósticas adicionales.

En general *Bacillus* spp. es sensible a aminoglucósidos, clindamicina, eritromicina, vancomicina, linezolid y carbapenémicos; como alternativas pueden emplearse quinolonas y doxiciclina. *B. licheniformis* es frecuentemente resistente a betalactámicos por la producción de una penicilinasa [6].

A pesar de que en este caso no se descartó la presencia de micobacterias y que la especie *B. licheniformis* es ubicua, y, generalmente no patógena, se han descrito casos de infección en seres humanos, principalmente en inmunocomprometidos. Deberíamos tenerla presente como potencial causante de cuadros infecciosos de piel y partes blandas en personas sanas con algún antecedente epidemiológico relacionado (contacto estrecho con suelo o tierra) como es el caso que se expone en esta contribución.

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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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Is *Mycobacterium shimoidei* an under-recognized cause of tuberculosis-like disease?

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Sir,

Mycobacterium shimoidei is a non-tuberculous mycobacterium (NTM) that was first described in 1975 by Tsukamura *et al.* [1], when it was isolated in a respiratory infection of a Japanese patient. However, it did not gain species status until 1982. As most NTM, it is an opportunistic pathogen that can be found ubiquitously in the environment [2]. Its epidemiology and current burden disease are difficult to determine since NTM reporting is not mandatory in most countries.

A 45-year-old Spanish male suffering thrombocytosis ($568x10^3/\mu L$) and lymphocytosis ($5{,}03x10^3/\mu L$) was admitted to the hospital. The patient has been suffering from a persistent cough with expectoration for the last year, accompanied by nocturnal sweating and a 10-kg weight loss in the last 3 months. He did not suffer from dyspnea.

After an haematologic disease was rule out, further tests were performed. He tested negative for HIV, HAV, HBV, HCV, HDV, toxoplasmosis and Herpesvirus; IgG was positive for CMV, Rubella and VEB. The TC-Body showed cavitated lesions in both apical regions of the lungs, linked to bilateral pulmonary nodules that suggested endobronchial dissemination. On the apical-posterior segment of the upper left lobe, the lesion had thickened walls creating a hydro-aerial level.

As clinical background, he suffered a spontaneous pneumothorax as a child and was a smoker of 28 packets of cigarettes per year. He denied having any contact with a suspected or confirmed case of tuberculosis and he had not received the bacilli Calmette-Guerin vaccine. The tuberculine test returned negative.

Four sputum samples obtained in consecutive days were cultivated in Lowenstein-Jensen (BBL™ Lowestein-Jensen Medium Slant) and MGIT (BBL™ MGIT™ 7mL) mediums. Although the four auramine-based stained bacilloscopies were negative, MGIT was positive for the four samples respectively in their 18th, 20th, 32nd and 38th day of incubation.

An immunocromatography for detection of *Mycobacterium tuberculosis* complex (BD MGIT™ TBc Identification Test) and a PCR for *Mycobacterium tuberculosis* (Xpert® MTB/RIF - Cepheid®) were performed in two of the sputums - both returned negative.

Therefore, suspicion fell on an atypical mycobacterium. *Mycobacterium shimoidei* was identified in the four samples with GenoType Mycobacterium AS (HAIN LifeScience GmbH, Nehren, Germany). This identification was confirmed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker® Biotyper) with a score of 1.89. Susceptibility was performed at the Spanish National Microbiology Centre: the isolate was susceptible to capreomycin, ethambutol, ethionamide and kanamycin, and resistant to rifampicin, isoniazid, pyrazinamide and streptomycin.

The patient received ribabutin 150mg 2 tablets /24 h, ethambutol 400 mg 4 tablets /24 h and clarithromycin 500mg/12h and was discharged. Considering he was in danger of social exclusion due to the lack of financial resources, it was decided to apply the Directed Observed Treatment (DOT) of the Red Cross.

One month later, he had gained weight (7 kg) and the radiological images were remarkably better. He did not mention any significant secondary effects due to the medication. However, in all the three control sputum samples collected, *M. shimoidei* grew again.

In the day 60 of treatment, for the first time he did not show any symptoms and the blood test was normal. Another three sputum samples were collected and, 40 days later, they returned sterile. Treatment continued with DOT.

Clinical improvement continued throughout the following check-ups. Treatment was finally suspended after 17 months, one year since the first negative cultures for *M. shimoidei*.

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The lung images kept becoming better and the blood test results were in normal range. The patient went in his +30-day post-treatment to a final check-up. Despite the thorax x-ray still showed lingering lesions on the upper left lobe and the lingula, likely associated to the pneumothorax and the mycobacteriosis, the image had improved. Clinically, he showed no symptoms at all.

Although rarely reported, *M. shimoidei* has been described worldwide. It is known to produce tuberculosis-like symptoms, including fever, productive cough and weight loss [3]. Reports also declare lung cavitations as the most common radiographic finding [4]. It does not require an immunocompromised status, but it usually affects people with pre-existing lung diseases [5]. Treatment usually relies in *in vitro* susceptibilities and in previous experience: a 6-month regimen with ethambutol, rifabutin and clarithromycin has been proven effective [3].

Here we describe a successfully treated case of an immunocompetent patient that suffered with a tuberculosis-like disease. To our knowledge, this is the first report of *M. shimoidei* in Spain. NTM as causative agents of infections may be underrecognized and sometimes misidentified, but modern improvements in diagnostic techniques is leading to an increase in detections. In this line, performing molecular methods is fundamental for its correct identification. In cases with these clinical features and in absence of tuberculosis, we should always consider rare NTM in the differential diagnosis, especially due to their resistance to antimycobacterial treatment. Nevertheless, further studies should be performed to strengthen our knowledge of *M. shimoidei* and its repercussion in infection.

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CONFLICT OF INTEREST

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FUNDING

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CONFLICT OF INTEREST

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Definiendo nuevos escenarios terapéuticos para oritavancina: severa infección bacteriémica de piel y partes blandas por *Staphylococcus aureus* en una paciente oncológica intensamente inmunodeprimida

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Estimado Editor:

Oritavancina es un lipoglucopéptido semisintético de acción prolongada (LGP) con potente actividad bactericida frente a patógenos grampositivos [1,2]. Su uso está aprobado en infecciones agudas de piel y partes blandas (IPPB), y sus propiedades farmacocinéticas únicas sugieren un excelente papel en otras infecciones como las osteoarticulares y las bacteriemias [3,4]. Sin embargo, la experiencia clínica con *Oritavancina* en infecciones graves bacteriémicas es limitada y heterogénea con respecto a las indicaciones, los regímenes de dosificación y las poblaciones de pacientes [5,6]. Consideramos que uno de los escenarios clínicos más apremiantes en los que los LGP deben demostrar su valor añadido es el de las infecciones bacteriémicas en pacientes oncológicos e inmunodeprimidos.

Mujer de 59 años remitida desde un centro oncológico externo donde estaba siendo tratada de un cáncer microcítico de pulmón metastásico a columna mediante poliquimioterapia, encontrándose en remisión completa confirmada por PET-TC reciente. En las últimas semanas había desarrollado una polineuritis severa paraneoplásica con afectación grave de extremidades, por la que había sido tratada con dosis altas de metilprednisolona en pulsos y se encontraba pendiente de recibir gammaglobulinas endovenosas de forma inminente.

Tres semanas antes había sufrido una herida incisa profunda en el dedo índice de la mano derecha, que había sido tratada con diferentes antibióticos orales de amplio espectro. Debido a la débil respuesta inflamatoria local y sistémica por la intensa inmunodepresión de base, la gravedad de la situación fue probablemente infraestimada en la evolución, presentando empeoramiento progresivo de forma que en la valoración inicial en nuestro centro presentaba el aspecto físico ilustrado en la Figura 1.1 y 1.2. En la exploración presentaba febrícula (37,6ºC) y estabilidad hemodinámica. No se auscultaban soplos y el Port-a-Cath no presentaba signos sospechosos de infección. En la analítica destacaban 4.550 leucocitos/µl, VSG 98 mm/h, creatinina 0,97 mg/dl, ALT 21 U/L, LDH 272 U/L, ferritina 994 ng/ml, IST 4%, PCR 11,8 mg/dL, con coagulación y gasometría normales. Los estudios de imagen mediante TC total body y ecocardiografía descartaron endocarditis e implantes sépticos hematógenos.

Se cursaron hemocultivos y una muestra de exudado purulento mediante inyección profunda, y nos pusimos en contacto con el Servicio de Traumatología para programar con carácter preferente la cirugía de drenaje y reconstrucción de la mano, que se realizó a las +36 h del ingreso. Precisó desbridado por doble vía de abordaje ante el hallazgo de tenosinovitis supurativa de las vainas de los extensores y los flexores del antebrazo, drenaje del gran absceso en cara dorsal de la palma y amputación por necrosis de la falange FII 2º dedo. Se realizó Flap cutáneo palmar, y se dejaron drenajes Penrose en las vainas flexora y extensora del 2º dedo, y en la comisura proximal de ambas heridas dorsal y palmar (Figura 1.3 y 1.4).

En este escenario inicial complejo e infrecuente de IPPB complicada en una paciente oncológica intensamente inmunodeprimida que necesitaba someterse a un nuevo tratamiento inmunosupresor, se nos planteó el dilema del antimicrobiano a elegir cuando obtuvimos a las 24 horas el resultado del cultivo del exudado de la herida -*Staphylococcus aureus* sensible a meticilina, aislándose 24 horas después la misma cepa en cada uno de los tres hemocultivos cursados inicialmente, confirmándose la situación bacteriémica.

Si nuestra paciente hubiese sido considerada inmunocompetente sin otra comorbilidad determinante, nos hubiésemos decantado probablemente por cefazolina vs cloxacilina endovenosas combinadas con daptomicina, ceftarolina o fosfomicina, buscando sinergias dada la gravedad de la presentación del cuadro. En nuestra paciente inmunodeprimida intensa, con vías venosas periféricas impracticables, portadora de Port-a-Cath, con alto riesgo de infección nosocomial, y con necesidad de continuar lo antes posible con un tratamiento inmunosupresor,

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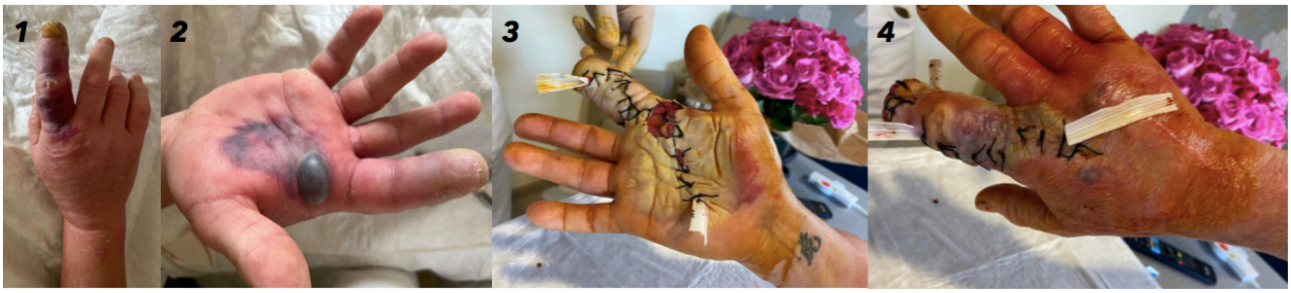

Figura 1 | **1 y 2: Día 0. Situación al ingreso (noviembre 2022). 3 y 4: Día +4. 24h después de la cirugía.**

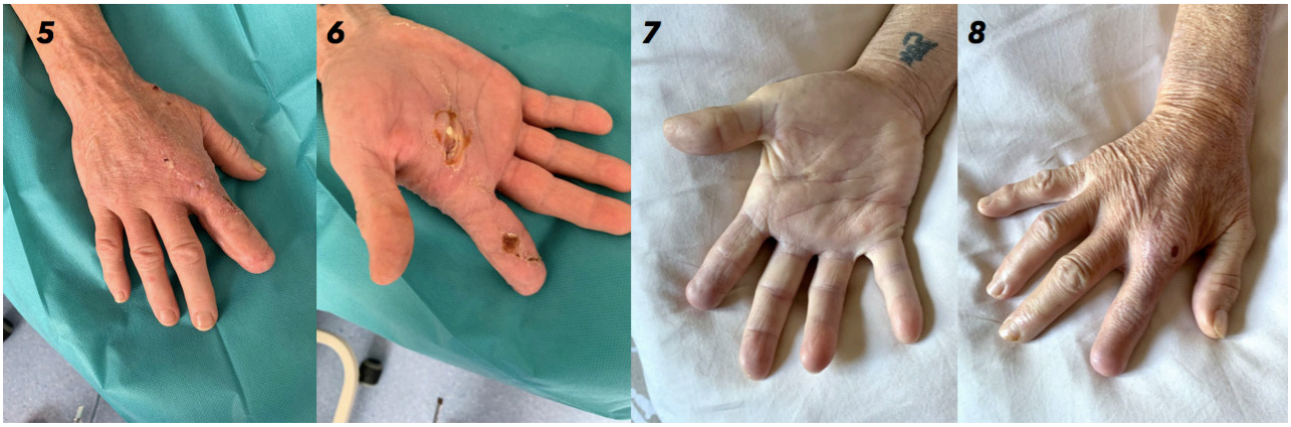

Figura 2 | **5 y 6: Día +35. Revisión en Consultas Externas (enero 2023). 7 y 8: Situación actual (abril 2023).**

decidimos que el antibiótico a seleccionar debía cumplir estos requisitos: amplia y prolongada difusión en tejidos blandos, eficaz en situaciones de bacteriemia, rápida e intensa acción bactericida y óptima dosificación.

Nos decantamos por oritavancina, en dosis única de 1200 mg, asociando cotrimoxazol y fluconazol orales para la prevención primaria de otras infecciones oportunistas durante todo el proceso de tratamiento inmunosupresor intensivo subsiguiente. La tolerancia fue buena, no observamos secundarismos (naúsea, cefalea). Los hemocultivos de control a las 48 horas fueron negativos. La paciente resultó alta hospitalaria en el día +11, continuando curas ambulatorias (Figura 2.5 a 2.8) y todo su proceso de tratamiento oncológico, manteniéndose la enfermedad en remisión completa en abril de 2023.

Como se observa con frecuencia con los nuevos antimicrobianos, oritavancina y el resto de LGP se han aprobado inicialmente para el tratamiento de infecciones en las que los clínicos no se enfrentan a necesidades críticas. Tras revisar la literatura disponible y según nuestra experiencia pensamos que el uso de un LPG como oritavancina es particularmente atractivo en las IPPB estafilocócicas bacteriémicas cuando se desea una terapia intensa y prolongada [7], buscando el alta hospitalaria precoz [8,9] evitando utilizar un dispositivo central, y más aún si cabe, cuando el paciente es oncológico, está intensamente inmunodeprimido en una situación clínica en la que no hay margen para el fracaso terapéutico inicial ni para la demora en los tiempos de actuación.

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Estudio comparativo de dos métodos de detección frente al virus Monkeypox: antígeno y PCR

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El virus de la viruela símica (Monkeypox, MPX) fue identificado en 1958. Es un virus ADN doble cadena del género *Orthopoxvirus*. La vía de transmisión más conocida es el contacto estrecho con lesiones de la piel.

En abril de 2022 apareció un brote en la Comunidad de Madrid, con un elevado número de casos, lo que hizo ver la importancia de contar con técnicas de diagnóstico rápido para poder frenar su transmisión [1,2].

Por ello, el objetivo del estudio es evaluar la utilidad del test de antígenos *Dynamiker Biotechnology* (Tianjin) Co., Ltd. para detectar el MPX, frente a los resultados obtenidos por la PCR en tiempo real RealStar® *Orthopoxvirus* de Altona Diagnostics (de referencia), y el sistema STANDARDTM M10 MPX/OPX SD BIOSENSOR.

Para llevarlo a cabo se utilizaron 20 muestras (10 sueros y 10 exudados de úlceras mucocutáneas) de pacientes con sospecha de infección por MPX. Se analizaron con PCR-RT de Altona [3,4] y mediante el test de antígenos *Dynamiker Biotechnology*. Las 10 muestras de exudado de lesión se analizaron además mediante PCR-RT de BIOSENSOR. Todas las técnicas se realizaron siguiendo las instrucciones del fabricante [5-7]. Las muestras eran de pacientes varones, con una edad media de 37 años (comprendidos entre 24 y 63 años), procedentes de diversas localizaciones geográficas (Latinoamérica, España y Europa Occidental), y que referían fundamentalmente practicar sexo con hombres (HSH).

En cuanto a los resultados de la PCR de Altona, 10 muestras resultaron positivas (9 exudados y 1 suero), mientras que solo 5 muestras (3 exudados y 2 sueros) fueron positivas con los test de antígenos *Dynamiker Biotechnology* (Tabla 1).

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La baja carga viral que se encuentra en la sangre de los pacientes infectados podría explicar los resultados negativos obtenidos en las muestras de suero tanto por PCR (9; 90%) como por los test de antígenos (8; 80%), a pesar de sí resultar positivos en las muestras de lesión por la mayor carga viral en estas localizaciones [3,4].

Dadas las peculiaridades de algunos pacientes, la rapidez en el diagnóstico es un factor a tener en cuenta. En este sentido, la posibilidad de contar con un test de antígenos que ofrezca un resultado fiable en menos de 20 minutos es una idea atractiva.

Los datos de este trabajo, aunque realizados con un pequeño número de muestras, parecen indicar que, en este momento, los test disponibles no son una buena opción.

En la Tabla 1 se resumen los cálculos estadísticos de sensibilidad, especificidad, valor predictivo positivo y negativo, donde podemos ver que el valor de falsos negativos es bastante elevado. Por ello, estos test podrían servir para descartar positivos en exudados, pero los negativos tendrían que analizarse por una técnica más sensible, como la PCR.

Las muestras de exudado de lesión se analizaron también mediante la PCR de BIOSENSOR, obteniéndose, en todos los casos, resultados positivos (Tabla 1).

Como puede observarse, obtuvimos un resultado positivo para una de las muestras que había dado negativa con PCR de Altona, por lo que debería considerarse como un falso positivo.

No obstante, cabe resaltar que este paciente presentaba clínica compatible con infección por MPX (úlcera genital), y que el resto de las pruebas realizadas por protocolo (PCR rectal y de úlcera genital para despistaje de otras infecciones de transmisión sexual, y serología) fueron también negativas; y que en un nuevo episodio, dos meses más tarde, fue diagnosticado de MPX en exudado faríngeo.

Se ha comprobado que el MPX puede permanecer durante semanas en diferentes localizaciones (41 días en lesiones cu-

Tabla 1 **Resultados de la PCR-RT RealStar® *Orthopoxvirus* de Altona, PCR-RT STANDARD™ M10 MPX/OPX SD BIOSENSOR y test de antígenos Dynamiker Biotechnology (Tianjin) Co., Ltd.**

	PCR Altona (Ct)	Test de antígenos	PCR BIOSENSOR (sonda OPX)	PCR BIOSENSOR (sonda MPX)
Exudados				
1	Positivo (20,4)	Negativo	Positivo	Positivo
2	Positivo (22,48)	Negativo	Positivo	Positivo
3	Positivo (21,16)	Positivo	Positivo	Positivo
4	Positivo (22,36)	Negativo	Positivo	Positivo
5	Positivo (23,72)	Negativo	Positivo	Positivo
6	Negativo	Negativo	Positivo	Positivo
7	Positivo (19,9)	Negativo	Positivo	Positivo
8	Positivo (18,59)	Positivo	Positivo	Positivo
9	Positivo (23,22)	Positivo	Positivo	Positivo
10	Positivo (27,8)	Negativo	Positivo	Positivo
Sueros				
11	Negativo	Positivo	ND[1]	ND[1]
12	Negativo	Negativo	ND[1]	ND[1]
13	Negativo	Positivo	ND[1]	ND[1]
14	Negativo	Negativo	ND[1]	ND[1]
15	Negativo	Negativo	ND[1]	ND[1]
16	Negativo	Negativo	ND[1]	ND[1]
17	Negativo	Negativo	ND[1]	ND[1]
18	Positivo (34,23)	Negativo	ND[1]	ND[1]
19	Negativo	Negativo	ND[1]	ND[1]
20	Negativo	Negativo	ND[1]	ND[1]
		Sensibilidad: 30% Especificidad: 80% VPP: 60%; VPN: 53% FP: 20%; FN: 70%	Sensibilidad: 100%; VPP: 90%; FN: 0% Especificidad; VPN y FP: ND[2]	

Ct: umbral de ciclos o cycle threshold. El resultado de la PCR se considera negativo con Ct > 40. [1]ND; no determinado. [2]ND; no determinado por falta de resultados negativos en el estudio. VPP: valor predictivo positivo; VPN: valor predictivo negativo; FN: falsos negativos; FP: falsos positivos

táneas y 39 días en semen), por lo que el resultado obtenido con BIOSENSOR podría ser un positivo real, que indicaría mayor sensibilidad de esta técnica, debido probablemente a la utilización de dos sondas para la detección del MPX [3,4,8].

A pesar del resultado discrepante entre las dos PCRs, los datos de nuestro estudio muestran que las PCRs probadas son una buena opción para detectar el MPX. La de BIOSENSOR ofrece la ventaja de ser más rápida si bien, como punto negativo, cabe destacar que las muestras solo pueden procesarse de una en una, frente al multianálisis que ofrece la PCR de Altona.

No debemos olvidar, que aunque parece que el control del brote inicial del MPX está controlado, y que no se ha vuelto a producir un número de casos importante, la posibilidad de contar con un método rápido y fiable es fundamental para la detección de los mismos y sobre todo, poder reducir la transmisión.

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CONFLICTO DE INTERESES

Los autores no presentan ningún conflicto de intereses.

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Uveítis complicada por *Scedosporium apiospermum* sensu estricto: relevancia del diagnóstico precoz y su manejo multidisciplinar

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Paciente varón de 63 años de edad sin antecedentes sistémicos ni oculares que acude al servicio de urgencias presentando un cuadro de ojo rojo doloroso acompañado de fotofobia de días de evolución con agudeza visual conservada. A la exploración se observan células inflamatorias en cámara anterior junto con un mínimo defecto epitelial no infiltrado (1x1mm). Se diagnostica de uveítis anterior aguda y se comienza tratamiento tópico con colirio de dexametasona 1mg/ml y ciclopentolato 10mg/ml junto con ofloxacino 5mg/ml, para evitar sobreinfecciones del defecto epitelial.

En la revisión a la semana el paciente no presenta mejoría de la inflamación intraocular pero sí un aumento de tamaño del defecto epitelial sin apreciarse ningún signo de infiltrado corneal. Se intensifica la pauta antiinflamatoria y profiláctica añadiendo pomada nocturna de Terracortril® (oxitetraciclina 5mg/g, hidrocortisona 10mg/g, polimixina B 10000U/g). Se reevalua al paciente a las 48 horas, cuando se aprecia por primera vez un infiltrado corneal de 4x4.5mm, hipopion menos de 1mm y pliegues estromales junto con la reacción inflamatoria ya conocida en cámara anterior. Tras una anamnesis más detallada el paciente refiere haber estado realizando tareas de campo los días anteriores.

Se contacta en ese momento con el laboratorio de Microbiología para toma de muestras solicitando cultivo de bacterias y hongos. Tras informe de la tinción de Gram ese mismo día (Figura 1A) se retiran los corticoides y se pautan colirios fortificados para bacterias (vancomicina 50mg/ml y ceftazidima 50mg/ml, 1 gota cada dos horas sin descanso nocturno) y tratamiento empírico para queratomicosis con colirio fortificado de voriconazol al 1% horario (10mg/ml), al no disponer de natamicina al 5%. Se añadió al tratamiento voriconazol oral (400 mg/12 horas las primeras 24 horas, luego 200 mg/12 horas).

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El raspado corneal fue inoculado en agar sangre, chocolate, Sabouraud cloranfenicol y BHI (Brain Heart Infusion), incubándose a 35ºC. A las 48 horas se observa en todas ellas un crecimiento de colonias algodonosas, con tonalidad blanca en el borde y gris verdoso en el interior (Figura 1B).

Se llevó a cabo una primera identificación mediante la técnica de azul algodón de lactofenol, en el que se observaron hifas hialinas, septadas, con conidióforos largos que soportan conidios individuales, ovalados, únicos y de base truncada. Según la observación microscópica, la presencia de graphium (Figura 1C) y ausencia de pigmento difusible amarillo en el agar, nos hizo sospechar la presencia de *Scedosporium apiospermum* complex.

Tras la imposibilidad de poder concluir la especie, se deriva a nuestro centro de referencia para realizar la técnica de biología molecular, siendo identificado como *Scedosporium apiospermum sensu estricto*. La sensibilidad fue testada mediante CMI, anfotericina B 16 mg/L, itraconazol >8 mg/L, voriconazol 2mg/L, posaconazol >8 mg/L, isavuconazol >8 mg/L, terbinafina >16 mg/L, caspofungina 1 mg/L, micafungina 0,12 mg/L, anidulafungina 0,03mg/L.

El paciente evoluciona de forma tórpida, con fluctuaciones en el tamaño del hipopion, infiltrado estable en tamaño y con aclaramiento progresivo, aunque con inicios de melting corneal (Figura 2A); por lo que se añade vitamina C oral 1 g/24h, doxiciclina oral 100 mg/12 horas y colirio de suero autólogo al 20%/6 horas en un intento de frenar la lisis colágena. Al mes del inicio del cuadro se empieza a conseguir una mejoría clínica con aclaramiento del infiltrado y la casi total resolución del hipopion. Sin embargo, el paciente acude a urgencias semanas después presentado dolor agudo tras un esfuerzo. Con el diagnóstico de perforación corneal se decide realizar una queratoplastia penetrante de urgencia en caliente, con inyección intracamerular de voriconazol (100 µg/0,1ml) y anfotericina B (0,05 mg/ml), consiguiéndose resecar completamente el infiltrado. El paciente siguió tras la cirugía una terapia antiinflamatoria con colirio de dexametasona (1 mg/ml) en

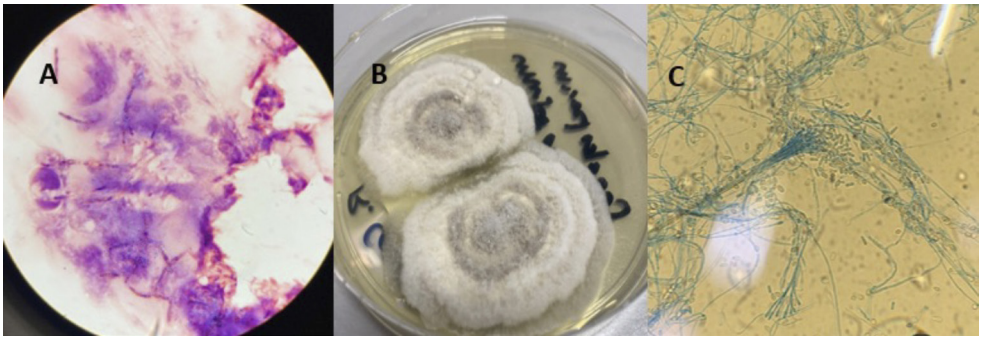

Figura 1 | **A: Estructuras fúngicas en la tinción de Gram. B: Colonias en agar Sabouraud. C: Técnica azul de algodón de lactofenol, observación microscópica del graphium**

pauta descendente, voriconazol tópico 1% cada 6 horas profiláctico y lubricación abundante para cuidar la superficie ocular. Se envía la córnea al laboratorio de Microbiología aislándose nuevamente *Scedosporium apiospermum sensu estricto,* con idéntica CMI para el voriconazol.

A los tres meses de la intervención la presión ocular se mantiene normal en 10 mmHg y la agudeza visual en 0.3, con puntos corneales in situ y sin signos de recidiva infecciosa (Figura 2B).

Las queratomicosis son infecciones fúngicas, supurativas y ulceradas, cuya prevención y tratamiento son difíciles de abordar. Pueden producir daños devastadores, incluso pérdida del globo ocular, si se deja que progresen sin control.

En países desarrollados, la queratitis fúngica filamentosa suele producirse en hombres sanos que se dedican a trabajos agrícolas, como consecuencia de traumatismo con materia vegetal contaminado con esporas fúngicas, que se implantan en el estroma corneal [1-2]. Otros factores de riesgo incluyen anomalías corneales, inmunosupresión local por uso de corticoides, empleo de soluciones o lentes de contacto contaminadas, cirugía ocular previa o trastorno sistémico [2]. En el caso que nos ocupa, al rehistoriar al paciente, confirmó el antecedente de traumatismo con materia vegetal durante una poda.

En el seno de inflamación corneal sospecharemos una etiología fúngica, cuando el curso sea lento, tórpido, presente una úlcera de aspecto radiado (plumoso), lesiones satélites e hipopion recurrente [2,3]. Aunque el diagnóstico de sospecha es clínico, es necesario filiar rápida y certeramente el agente etiológico responsable, con un adecuado raspado corneal [4]. En casos donde se reepiteliza el epitelio tras el trauma y la queratitis tiene lugar en el interior del tejido estromal, puede ser necesaria la biopsia corneal.

En nuestro paciente fue determinante el hecho de realizar la tinción de Gram del raspado corneal, donde se observaron hifas septadas, lo que permitió el ajuste del tratamiento. El examen directo es barato, simple y rápido y aunque es posible observar estructuras fúngicas con KOH, se prefiere usar tinciones como el Gram, Giemsa o blanco de calcoflúor [4]. El diagnóstico de confirmación continúa siendo el cultivo [4-5]. El material obtenido generalmente es escaso y debe ser sembrado directamente en la propia cabecera del enfermo, en medios de cultivo para bacterias, hongos, virus o *Acanthamoeba* (si existe sospecha clínica). La mayoría de los hongos oculares crecen en 2 o 3 días, aunque es prudente esperar dos semanas, para descartar su presencia [3]. Sin embargo, un cultivo negativo no descarta el diagnóstico de presunción, debido a que no tiene el 100% de sensibilidad.

Dentro de los hongos miceliales implicados, *Fusarium* y *Aspergillus* son los aislados con mayor frecuencia. En cuanto a las especies de *Scedosporium* son más inusuales de encontrar entre los causantes de queratitis [6]. El primer caso de queratitis por *Scedosporium* fue descrito en 1955 [7] y continúa siendo inusual. Dentro de dicho género, las especies con mayor relevancia clínica para el hombre son: *S. apiospermum, S. boydii, S. aurantiacum, S. dehoogii y S. minutisporum* [8]. La presencia de sinnemas o graphium puede ser observada en todas excepto *S. dehoogii*. Destaca *S. apiospermum* complex como el más frecuente en nuestro medio. Los métodos fenotípicos convencionales son bastante limitados para la diferenciación de las diferentes especies, así que llevar a cabo una identificación precisa, requiere enfoques moleculares en la mayoría de las ocasiones [9].

En nuestro paciente se aisló *Scedosporium apiospermum sensu* estricto. Un hongo de distribución mundial, aislándose en suelo, plantas, agua dulce y estancada. La posibilidad de encontrarlo en estos lugares, sumado a la capacidad del hongo de diseminación, favorece el compromiso de la vía ocular o la vía respiratoria [10].

El estado inmunitario de los pacientes juega un papel muy importante. En pacientes inmunocompetentes se desarrollan normalmente infecciones locales como son las infecciones cutáneas, micetoma, otitis, infecciones osteoarticulares y oculares. Sin embargo, en pacientes inmunodeprimidos, se han descrito casos de infección profunda, infecciones diseminadas, endocarditis, infecciones del SNC, infecciones respiratorias similares a aspergilosis, así como casos de enfermedad broncopulmonar alérgica [11].

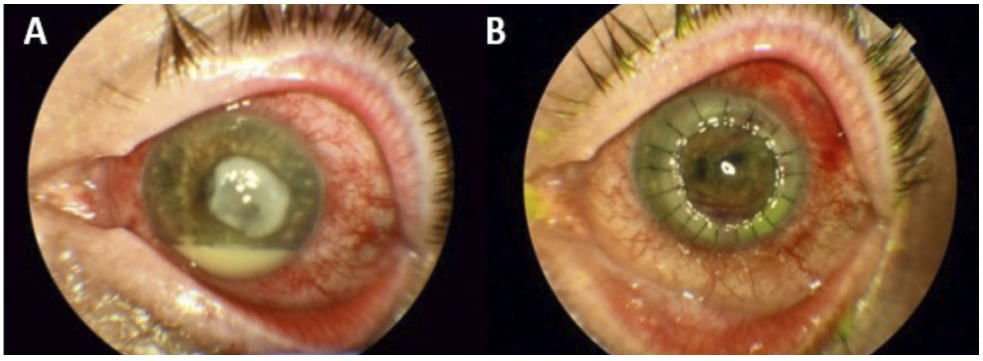

Figura 2 | **A: Imagen ocular tras 15 días de tratamiento, donde se observa la lesión corneal e hipopion. B: Imagen tras queratoplastia penetrante.**

Las infecciones oculares causadas por el complejo de especies de *S. apiospermun* son infrecuentes, siendo las presentaciones más comunes la queratitis (84,6%) y la escleroqueratitis (15,3%) [12]. Los pacientes suelen tener un pronóstico visual desfavorable con una baja probabilidad de conservación del órgano, debido al retraso en el diagnóstico o mala respuesta a los antifúngicos [2]. Sin embargo, si se detecta rápidamente, se instaura una pauta de tratamiento adecuada y se asegura un buen cumplimiento de la misma, aumenta mucho las probabilidades de éxito.

Tras establecer el diagnóstico, se debe tratar la queratitis con antifúngicos tópicos pautados en intervalos cortos de tiempo. El tratamiento de elección para infecciones por *Scedosporium* spp, según las guías internacionales es el voriconazol [13]. Es obligatorio realizar el estudio de sensibilidad in vitro, aunque no están establecidos los puntos de corte clínicos en este género. Sin embargo, su interpretación posibilita una terapia racional.

La pauta ideal, consiste en administrar colirio fortificado de voriconazol al 1%, 1 gota cada hora durante las primeras 48 horas. Si existe respuesta clínica se puede plantear, aplicarlo cada 2 horas, respetando el descanso nocturno. La duración del tratamiento antifúngico tópico no está bien establecida, aunque es larga (habitualmente 6 semanas para *Candida* spp y 12 semanas para los hongos filamentosos) [3]; debiendo prolongarse 3 semanas después de la aparente curación clínica [14]. Esto requiere una vigilancia estrecha para ir reduciendo gradualmente los fármacos. En caso de baja respuesta clínica podría optarse por el uso de inyección intraestromal o intracamerular con un máximo de 4 inyecciones en intervalos de 72 horas [15].

El tratamiento sistémico debería considerarse en pacientes con lesiones severas y en todo paciente inmunodeprimido, siendo voriconazol de elección debido a sus características farmacocinéticas y farmacodinámicas (dosis de carga 400mg cada 12 horas el primer día, seguido de 200-300 mg cada 12 horas; en pacientes de >40 kilos de peso) [14]. Para asegurar que las concentraciones son óptimas, se determinan los niveles séricos en el valle, entre los 5 y 7 días del inicio el tratamiento oral [16].

A pesar de haber introducido el antifúngico de elección (tópico y oral) desde el diagnóstico microbiológico, se produjo una perforación ocular que llevo a una queratoplastia penetrante. Habiendo sido descartadas la falta de sensibilidad al voriconazol y las concentraciones plasmáticas insuficientes de dicho fármaco (4.73 µg/ml en el valle).

Sigue habiendo un alto porcentaje de fracaso terapéutico; el escenario futuro podría mejorar con la incorporación de nuevas técnicas diagnósticas y el desarrollo de nuevos fármacos. El microscopio confocal es una técnica no invasiva, subjetiva y útil en el caso de queratitis fúngicas y por *Acanthamoeba* [7,17]. Por otro lado, en el laboratorio de microbiología, las técnicas de biología molecular, presentan una alta sensibilidad y especificidad, permitiendo acortar el tiempo de respuesta a 4-8 horas frente a los 15 días del cultivo [4]. Sin embargo, ambas no se encuentran implantadas en la práctica clínica, debido a su coste.

En lo que respecta a los nuevos antifúngicos, parece prometedor el uso de olorofim en la escedosporiasis. El fármaco actúa ejerciendo la muerte celular fúngica mediante la inhibición de la enzima dihidroorotato deshidrogenasa (DHODH) en la vía de la síntesis de la pirimidina [18]. La comercialización de olorofim sigue pendiente de la aprobación por parte de la Agencia Europea del Medicamento (EMA) y la *Food and Drugs Administration* (FDA).

A modo de conclusión, el pronóstico de las queratomicosis depende la rapidez con la que se instaure un tratamiento específico, lo que requiere una estrecha colaboración oftalmólogo y microbiólogo para determinar con certeza la etiología de los procesos supurativos corneales, donde la tinción de Gram nos aporta un gran valor.

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Letter to the Editor

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Association of nirmatrelvir/ritonavir and remdesivir as treatment for SARS-CoV-2 infection in immunocompromised patients with hematologic malignancies. Series of four cases

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Sir,

The choice of treatment against SARS-CoV-2 infection in patients with hematologic malignancy with active drug therapy is challenging, given the absence of randomized studies in this patient profile. In addition, the behavior of the virus in this group is different, with evidence of sustained viral replication over time [1]. In this regard, there have been reports of viral persistence and even recurrent pneumonia, especially in patients with hematological malignancies who have received treatment with anti-CD20 drugs in the 6 months prior to infection [2]. In addition, systemic corticosteroids could favor recurrence by decreasing viral clearance [3].

For its treatment, antivirals such as nirmatrelvir/ritonavir or remdesivir have been used in monotherapy, even in extended regimens, with different results [4,5]. Good results have also been reported in vitro and in vivo, in this subgroup of patients, with the combination of antivirals (nirmatrelvir/ritonavir and remdesivir) and even monoclonal antibodies [6-8].

In this context, and following a decision by a multidisciplinary committee for therapy against SARS-CoV-2, it was agreed to select those patients with hematological neoplasia under active treatment who could benefit from antiviral bitherapy, given the clinical suspicion of viral persistence and failure of previous antiviral monotherapy. The experience is described below.

Four patients (median age 65 years, interquartile range [IQR] 58-73) with oncohematologic disease on active treatment required admission for Covid-19 during 2022 (Table 1); two of them had pneumonia. In all of them, rituximab was part of the therapeutic regimen. The complete vaccination regimen had been administered in all patients, with the development of IgG anti-S antibodies against SARS-CoV2 in one of the cases (this was not analyzed in the remaining patients). Definitive antiviral treatment with concurrent antiviral bitherapy (nirmatrelvir/ritonavir and remdesivir) for 5 days was administered after having received, in all four cases, one or two full 5-day regimens of nirmatrelvir/ritonavir. The timing of administration was late in all cases, with a median of 48.5 days of symptoms ([IQR] 19.5-117). Although three of them did not have respiratory failure at the time of treatment, it is noteworthy that patient 3 had previously been admitted to the intensive care unit (ICU) for severe respiratory failure. Regarding the SARS-CoV-2 variant, in two patients it was confirmed by sequencing that the variant at the onset of symptoms and the variant prior to the start of antiviral bitherapy were the same, confirming the persistence of the infection despite prior antiviral monotherapy. In patient 1 it could not be confirmed since only the variant at symptom onset (Ómicron BQ.1.1.; variant derived from BA.5) was sequenced and prior to the start of bitherapy a rapid test (VIASURE SARS-CoV-2 Varian III Real Time PCR Detection Kit) was performed which confirmed the presence of the Q954H gene and not of A2710T, a finding common to Ómicron BA.2, BA.4 and BA.5.

Only one patient required ICU admission after bitherapy: he was admitted with pneumonia and severe respiratory failure and required non-invasive mechanical ventilation. After a slight improvement, he was transferred to the conventional hospital ward, at which time antiviral bitherapy was administered in view of the slow improvement and persistence of positive CRP with low Kt. Finally, he presented a new respiratory worsening and died. The remaining 3 patients responded effectively to the administration of this treatment, and only one of them died after 4 months due to progression of his hematologic disease. They also did not require new admission due to recurrence of the infection, nor new antiviral treatment, and

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Table 1 **Clinical cases that have received remdesivir and nirmatrelvir/ritonavir as antiviral bi-therapy.**

	CASE			
CLINICAL CONTEXT	1	2	3	4
Age (years)	55	69	77	61
Sex	Female	Male	Male	Male
Hematological malignancy (treatment line)	DLBCL (third line, CART therapy approved)	Mantle cell lymphoma (fourth line)	DLBCL (first line)	Mantle cell lymphoma (fourth line)
Treatment (time from last dose to onset of symptoms)	Rituximab Gemticitabine Oxaliplatine (2 weeks)	Rituximab Bendamustine (3 months)	Rituximab Cyclophosphamide Adriamycin Vincristine Prednisone (2 weeks)	Rituximab (5 weeks)
IgG anti-S against SARS-CoV-2	Yes	Unknown	Unknown	Unknown
Admission during which bitherapy antiviral treatment was administered	1st	1st	1st	2nd
Previous antiviral treatment (days)	Nirmatrelvir/ritonavir (1º 4 days) (2º 5 days)	Nirmatrelvir/ ritonavir (1º 5 days) (2º 5 days)	Nirmatrelvir/ritonavir (5 days)	Nirmatrelvir/ritonavir (5 days)
Virus variant at the onset of symptoms	Omicron BQ.1.1 (sequenced)	Omicron BA.5.2 (sequenced)	Omicron BQ.1.1.4 (sequenced)	Omicron BA.5.2 (sequenced)
Virus variant before bitherapy treatment	Omicron BA.2, BA.4 or BA.5[a]	Omicron BA.5.2 (sequenced)	Unknown	Omicron BA.5.2 (sequenced)
Ct prior to starting antiviral bitherapy	22	21	11	25
Days from symptom onset to administration of biotherapy treatment	23	74	16	199
Days from end of last antiviral treatment to starting antiviral bitherapy	11	10	9	194
Oxygen therapy at the time of biotherapy treatment	Room air (FiO_2 21%)	Room air (FiO_2 21%)	Nasal cannula (FiO_2 28%)	Room air (FiO_2 21%)
Maximum oxygen after bitherapy treatment	Room air (FiO_2 21%)	Room air (FiO_2 21%)	Helmet CPAP (FiO_2 60%)	Room air (FiO_2 21%)
Days of systemic corticosteroid treatment before definitive antiviral treatment	No	No	30	No
COVID-19 pneumonia	No	No	Yes	Yes
SARS-CoV-2 vaccination schedule	2 doses	2 doses	2 doses + 1 booster	2 doses
CLINICAL OUTCOMES				
Admission to ICU after administration of bitherapy treatment	No	No	Yes[c]	No
Hospital readmission after bitherapy treatment	Yes[b]	No	No	No
Days from initiation of bitherapy treatment to RT-PCR negative result	6	5	–	–
Death after administration of bitherapy treatment	Yes[b]	No	Yes[d]	No
Days of follow-up from last hospital discharge to end of study[e]	130	159	16	110

Abbreviations: CPAP, continuous positive airway pressure; DLBCL, diffuse large B-cell lymphoma; FiO2, inspiratory oxygen fraction; mAbs, monoclonal antibodies; ICU, intensive care unit.

[a]Obtained by "VIASURE SARS-CoV-2 Varian III Real Time PCR Detection Kit", a rapid test that detected the existence of the Q954H gene and the absence of the A2710T gene (high probability of being an Omicron BA.2, BA.4 or BA.5 variant; this gene is common to all three).

[b]The patient was admitted for progression of hematologic malignancy on March 7, 2023, with no clinical suspicion of persistence or recurrence of SARS-CoV-2 infection. On April 4, 2023 (4 months after RT-PCR negativation) he died due to his hematologic disease.

[c]Admission to the ICU during treatment with antiviral bitherapy.

[d]Died due to progression of respiratory failure secondary to SARS-CoV-2 infection.

[e]We consider 5/24/2023 as the current date.

they did not present symptoms related to COVID-19. In short, three of the four patients were not readmitted, nor did they die as a result of progression or relapse of the infection, nor did they require new antiviral treatment, and the infection was considered resolved. In addition, within a short period of time, the RT-PCR was negative for the first time (cases 1 and 2 6 and 5 days after the start of bitherapy, respectively; case 3 died and did not recur and case 4 did not have a control RT-PCR). Table 1 shows in more detail the clinical characteristics and the results obtained.

Despite being a very vulnerable group of patients, with previous failure to nirmatrelvir/ritonavir and on treatment with rituximab-based therapeutic schemes, 3 of the 4 patients responded satisfactorily after the administration of nirmatrelvir/ritonavir and remdesivir bitherapy. The remaining patient had a poor evolution, but it must be taken into account how advanced the disease was at the time of bitherapy administration. In short, the results obtained propose a new therapeutic alternative for oncohematological patients with difficulty in eliminating the virus. However, further studies are necessary to confirm this hypothesis.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Letter to the Editor

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Update on Bimervax® immunogenicity amplitude. Insights on humoral response against XBB.1.5 from an extension study (NTC05142553)

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Sir,

The World Health Organization (WHO) [1], in May 2023, and the European Medicines Agency (EMA) [2], in June 2023, published their recommendations on the composition of COVID-19 vaccines for the 2023-24 season. These recommendations, published after the acceptance of the manuscript, oblige the authors to produce a brief update and reinforce the Bimervax® vaccine positioning based on new evidence from the pivotal clinical trial (HIPRA-HH-2 extension, NCT05142553).

In 2023, COVID-19 cases have been mainly associated with the BQ and XBB.1.5 lineage variants, causing mostly mild cases, albeit also boosting hybrid immunity throughout the population. In early 2023, the XBB subvariant emerged and became predominant during the first semester of the year, accounting for around 90% of all variants in the winter period. Although in June XBB.1.5 still represented 75% of prevalent circulating sublineages, XBB.1.16 and XBB.2.3 appear to have been replacing it since April 2023.

The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) postulates that new COVID-19 vaccine formulations should seek to induce antibody responses that neutralize XBB Omicron descendent lineages [1]. One recommended approach is the use of a monovalent XBB.1 descendent lineage, such as XBB.1.5, as the vaccine antigen, although other formulations and/or platforms that achieve robust neutralizing antibody responses against XBB descendent lineages can be considered [1]. They also recommend moving away from the inclusion of the index virus in future COVID-19 vaccine formulations [1]. The EMA's Emergency Task Force recommends updating vaccines to target XBB strains, which have become dominant in Europe and other parts of the world [2]. The EMA and ECDC have also noted that monovalent vaccines (vaccines targeting a single strain, such as XBB.1.5) are a reasonable choice for providing protection against current dominant and emerging strains [2].

The HIPRA-HH-2 extension trial started in September 2022 (vaccination period up until December 2022), and data from 288 individuals vaccinated with a fourth dose of Bimervax® (PHH-1V) up until May 30, 2023, have been collected, coinciding with the period of maximum prevalence of the BQ and XBB.1.5 subvariants. On the cut-off date, only 34 (11.8%) individuals reported COVID-19, and no cases of severe disease, hospitalizations or death due to COVID-19 were recorded. Neutralizing antibody titers against XBB.1.5 were analyzed 14 days after the booster in all participants and at 3 months in individuals reporting mild infection during the study period.

The preliminary results (Figure 1; Table 1) show that a fourth dose of PHH-1V elicited a significant neutralizing antibody response against XBB.1.5 14 days after the booster (GMT= 284.32, GMFR=5.45). Compared to the humoral response induced by PHH-1V vaccination against previous variants [3], the XBB.1.5 neutralizing antibody levels are lower, which is in line with the results obtained with boosters with other vaccines against the XBB.1.5 subvariant [4-6]. However, in the same extension study, natural infection with the virus

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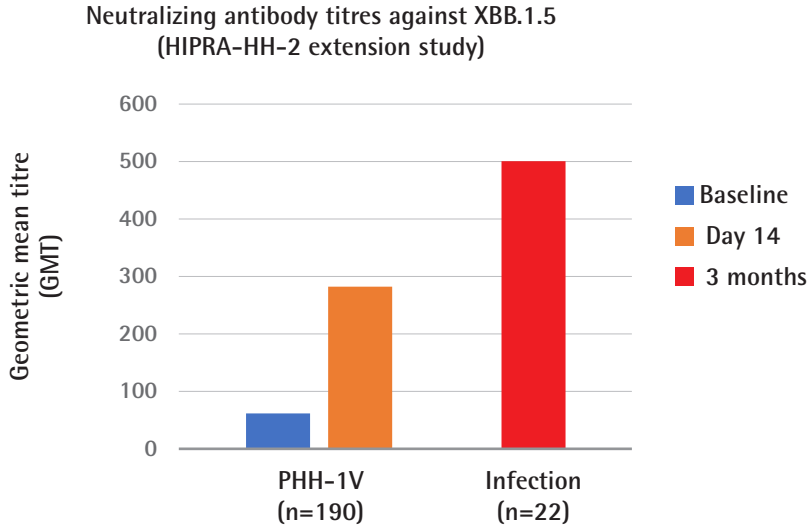

Figure 1 Geometric mean titer (GMT) of neutralizing antibodies against XBB.1.5 subvariant at baseline (blue bar) and day 14 (orange bar) after a boost with PHH-1V or after mild infection (red bar).

Table 1 Geometric mean titer (GMT) and Geometric Mean Fold Rise (GMFR) of neutralizing antibodies against the XBB.1.5 subvariant at baseline and 14 days after the 4th dose of PHH-1V. Neutralizing antibody levels (GMT) against the XBB.1.5 subvariant at 3 months in individuals reporting COVID-19 during the study period.

	HIPRA-HH-2 extension study (NCT05142553)		
	GMT at baseline (95% CI)	GMT at day 14 (95% CI)	GMFR (95% CI)
Study population (N=190)	52.18 (38.305, 71.078)	284.32 (208.685, 387.376)	5.45 (4.51, 6.58)
	GMT at 3 months (95% CI)		
Infected during study period (N=22)	500.11 (322.973, 774.386)		

CI: confidence interval

was also seen to elicit low XBB.1.5 neutralizing antibody levels (GMT=500.11, Figure 1; Table 1). In conclusion, both the Bimervax® vaccine (PHH-1V) and natural infection elicit a more discrete response compared to other variants, although considering the low percentage of individuals reporting infection (all mild), the response appears to be sufficient for protection from severe disease.

With the aforementioned results, this panel agrees on the capacity of PHH-1V booster immunization to induce a broad humoral response against emerging variants, including the 2023 circulating subvariants (XBB.1.5), as well as to provide protection from severe disease. Future strains for the 2023-2024 are not currently foreseeable, although based on the existing evidence on current and incoming vaccines, the HIPRA PHH-1V is still a robust option for COVID-19 vaccination boosting.

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