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Sumario

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Contents

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Volume 36
Number 3
June 2023

Contents

REVISTA ESPAÑOLA DE Quimioterapia

Volume 36
Number 3
June 2023

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Review

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Status of Herpes Zoster and Herpes Zoster Vaccines in 2023: A position paper

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ABSTRACT

Herpes zoster infection (HZ) is an important public health problem due to its high incidence and frequent complications, especially post-herpetic neuropathy . The incidence of HZ increases with age and is more frequent in immunocompromised patients. It is estimated that at least 60,000 people develop HZ each year in Spain.

The usual forms of HZ are so clinically characteristic that they do not usually require microbiological confirmation, which is reserved for cases without cutaneous manifestations or with atypical presentation.

There are currently two vaccines approved by the regulatory agencies and marketed in Spain to prevent the onset of HZ and its complications. The first (Zostavax®) was marketed by the company MSD and licensed in Europe in 2006 and is a live attenuated virus vaccine that is administered in a single dose, while the second (Shingrix®) is a recombinant vaccine, marketed in 2017 and requires two doses. While the former cannot be administered to immunocompromised persons, the latter can be prescribed to any group of adults.

The criteria for the indication and financing of these vaccines have not been uniform in the various autonomous communities of Spain.

These and other aspects of HZ have been discussed by a group of experts from the Illustrious Official College of Physicians of Madrid (ICOMEM) whose criteria and opinions are included in this paper.

Keywords: Zoster, Herpes zoster, Varicella-Zoster Virus, Postherpetic neuralgia, vaccines, Zostavax, Shingrix, Immunocompromised patients, elderly.

Situación del herpes zóster y de las vacunas contra el mismo en 2023: Un documento de opinión

RESUMEN

La infección por herpes zoster (HZ) es un importante problema de salud pública, por su elevada incidencia y frecuentes complicaciones; en especial la neuropatía post herpética. La incidencia de HZ aumenta con la edad y es más frecuente en inmunodeprimidos. Se calcula que, al menos, 60.000 personas desarrollan HZ cada año en España.

Las formas habituales de HZ son tan características clínicamente que no suelen requerir confirmación microbiológica que se reserva para casos sin manifestaciones cutáneas o con manifestaciones atípicas

En la actualidad, existen en España dos vacunas aprobadas por las agencias reguladoras y comercializadas para prevenir la aparición de HZ y sus complicaciones. La primera (Zostavax®) fue comercializada por la compañía MSD y autorizada en Europa en 2006 y es una vacuna de virus vivos atenuados que se administra en dosis única, mientras que la segunda (Shingrix®) es una vacuna recombinante, comercializada en 2017 y

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requiere dos dosis. Mientras la primera no puede ser administrada a inmunodeprimidos, la segunda puede administrarse a cualquier grupo de personas.

Los criterios de indicación y de financiación de estas vacunas no han sido uniformes en las diversas comunidades autónomas de España.

Estos y otros aspectos sobre HZ han sido discutidos por un grupo de expertos del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) cuyo criterio y opinión recogemos en este trabajo.

Palabras clave: Zoster, Herpes zoster, Virus Varicela-Zoster, Neuralgia Postherpética, vacunas, Zostavax, Shingrix, Inmunodeprimidos, ancianos

INTRODUCTION

Herpes Zoster (HZ) is a common disease caused by reactivation of the varicella-zoster virus (VZV), kept in a latent state since the primoinfection causing varicella (chickenpox). Its incidence is very high, particularly after the age of 50 years, to the point that more than around 20% of the global population will suffer one or more episodes of HZ if they live long enough to do so. The infection usually manifests as a cutaneous rash, characterized by the presence of vesicles evolving into crusts on the skin innervated by a central or peripheral nerve root. The disease usually progresses to spontaneous resolution but a proportion of patients will develop postherpetic neuralgia (PHN). The tendency to develop PHN or extracutaneous forms of the disease is all the greater in patients with various forms of immunosuppression.

The pharmaceutical industry has incorporated in the last 2 decades two effective vaccines against HZ of different nature and indications that are slow to be introduced in daily clinical practice and recommended by health authorities to large groups of the population.

The Scientific Committee on COVID-19 and Emerging Pathogens of the Illustrious College of Physicians of Madrid (ICOMEM) has asked itself a series of questions on the risks of HZ in different population groups, on the indications of vaccines against HZ, their contraindications, the potential for co-administration with other vaccines and on the variable response of the health authorities of the different autonomous communities of Spain in these circumstances.

We offer below the deliberation of the Committee on a series of issues that we consider of interest in the case of HZ, not only for the medical profession, but also for other health professionals and for the general population.

WHAT IS THE INCIDENCE OF ZOSTER IN THE WORLD AND IN SPAIN?

HZ infection is an important public health problem due to its high incidence and frequent complications, especially PHN. These translate into loss of quality of life and disability, largely due to the accompanying pain; in addition, HZ and PHN require a high use of health services and cause productivity losses.

Interestingly, the epidemiological characteristics of this disease vary little in the western world, as the incidence is quite similar between countries [1], and always increases with age and is more frequent in women, and in people with chronic diseases and reduced immunity (especially cellular). Probably, due to the increased survival of older people with such disorders, in the period 2009-2019, there has been an increase in the incidence of HZ in Spain from 75 years of age onwards [2].

Epidemiological surveillance of HZ is still under development, as data are not available for all the autonomous communities in Spain [3]. However, from the available information (the most recent is from 2018), at least 60,000 people develop HZ, and approximately 3,000 of them are hospitalized each year for this cause. About 50-60% of all those ill and hospitalized are over 60 years of age. In practical terms, the incidence of HZ in the adult population is very high, with more than one in five men and one in four women suffering from the disease between the ages of 50 and 85. The good news is that there is preliminary evidence that the incidence of HZ and its complications has declined somewhat in cohorts of children who have received the varicella vaccine [2] .

In a systematic review of the international literature, the risk of developing PHN ranged from 5% to more than 30%, depending on the type of study design, age distribution of the populations evaluated, and definition. More than 30% of patients with PHN experienced persistent pain for more than 1 year. The risk of recurrence of HZ ranged from 1% to 6%, with long-term follow-up studies showing an increased risk (5-6%) [4].

WHAT IS THE CLINICAL EXPRESSION OF VZV INFECTION?

VZV or Human Herpes Virus-3 (HHV-3), shares with the other close members of the *Alphaherpesviridae* subfamily the high transmissibility, the persistence in the host in latent form after infection and its capacity of reactivation with symptomatic clinical expression.

Primoinfection determines varicella as a clinical entity, a highly contagious process that affects practically the entire susceptible infant population and is characterized by a febrile condition followed by a rapidly evolving skin rash. Before the vaccine was introduced, only 10% of the population had chickenpox after the age of 13.

Once the disease has passed, generally without serious complications, VZV remains latent in the neuronal cells of the posterior ganglia of the spinal cord and brain, with minimal genomic expression. Its replication is contained by the immune system, which generates a long-lasting control [5].

The decrease of the immune response, due to any cause, allows the reactivation of the viral genetic material, with the consequent replication, invasiveness (cell to cell by continuity) and pathogenicity, giving rise to a second clinical form of the

disease that we call HZ or Herpes Zona (one virus, two clinical presentations) [5,6].

HZ, unlike varicella, predominates in the adult population (its overall incidence is 30%) and, as one gets older, the occurrence increases. Seventy percent of HZ appear after the age of 40 and one in two nonagenarians will have HZ at some point.

The latency state and possible reactivations of the virus that do not reach clinical expression are fundamental in maintaining the validity of immunity. It also appears that re-exposure to the virus by new infection has a role in maintaining immunity. However, after the drastic reduction of varicella with the generalized introduction of the varicella vaccine in the mid-1990s, it seems that the re-exposure to the virus by new infection plays a role in maintaining immunity [7]. The incidence of HZ does not seem to differ between countries where vaccination is the norm and where there is very little chickenpox [8] and, therefore, re-exposure by wild virus, and those where vaccination cannot or is not strictly enforced and chickenpox remains endemic [9]. This reinforces the idea that viral latency plays a key role in immune support [10].

HZ can be seen in healthy children, if the primary infection occurred very early. There is HZ in the first two years of age in children who were infected in their fetal period.

The attenuated viral variant Oka, used in the vaccine against varicella (chickenpox) [4], and later and with more viral load in the vaccine for HZ, has a behavior that determines a latency similar to the wild-type virus. Although it has less tendency to reactivation, it plays a similar role in the maintenance of immunity and, if this fails, it can mimic the primary disease (chickenpox) or HZ.

Immunosenescence and consequent loss of specific protection against the virus is the most common cause of HZ. Despite the boosting of immunity achieved by reactivation with clinical translation, a second episode of HZ can occur in up to 4% of patients and a third in 2%.

The most frequent complication is PHN, which appears in 5-20% of HZ (it increases in frequency and intensity with age). It is an inflammatory and cytopathic process in the neurons of the dorsal medullary ganglia and their corresponding axons that causes pain, sometimes very intense and of long duration. It is not known why some patients develop PHN and others do not. The intensity of the damage during the inflammatory phase, the production of neurotoxic substances, the existence of viral strains that alter conduction in the sodium channels of the nerve cell, the persistence of viral replication, and genetic and racial response factors have been postulated.

Neurotoxicity can, much less frequently, affect the anterior motor ganglion of the metameres, causing flaccid paralysis of the involved motor area. There are facial paralysis and paralysis of any other motor territory, including atonic bladders due to lesion of the sacral roots. Recovery is estimated at 50%. VZV can also produce myelitis, Guillain-Barré syndrome and meningoencephalitis.

VZV has three preferential cell tropisms in its invasiveness: T lymphocytes; skin epithelial cells and neurons. In its lymphocytic localization it is transported throughout the organism and can cause visceral complications (vasculitis, retinitis, enteritis...).

Vascular involvement, especially in the central nervous system, is a new field of study in the pathogenesis of VZV. The increase in stroke after an episode of HZ seems clear [11] and especially after the one that occurs with ocular lesion [11].

The identification of VZV in the wall of the temporal arteries has raised another question in the pathogenesis of temporal arteritis and has raised the issue of whether antivirals should be used in addition to corticosteroids for its treatment [11].

Ocular involvement (severe keratitis) and retinitis, sometimes necrotizing, are more frequent after HZ, and especially the latter is usually a complication clearly related to severe cellular immunosuppression states; HIV infection is a clear example [12].

Complications of infection or reactivation (varicella or zoster) may occur without the characteristic skin lesions, which should be taken into account as etiology before their appearance (meningoencephalitis, facial paralysis, stroke in children...).

WHAT IS THE BODY'S IMMUNE RESPONSE TO VZV AND HOW DOES IT EVOLVE THROUGHOUT LIFE?

The specificity of the virus for humans has made it difficult to understand the pathogenesis of the disease and the immune response. Only in recent years, and thanks to experimental models, has it been possible to deepen the molecular mechanisms of pathogenicity and cellular response to the virus [10].

VZV enters the body via the respiratory route and, through the nasopharyngeal epithelium, infects the lymphoid tissue of the pharynx [13] from where it is disseminated and transported in T-lymphocytes [14]. It finally invades the epidermal epithelium (symptomatic target of primoinfection) and by its own viraemia and probably by retrograde progression from the skin, through the sensory axons, it reaches the neurons of the posterior ganglia, where it remains resident under the control of the immune system. It has a long prodromal period (10 to 21 days), during which it is able to evade the defensive response, partially inhibiting functions of the innate immune response [15]. Once this is overcome, it induces cellular damage and the inflammatory response occurs, where it is the specific cellular immunity (mediated by T lymphocytes) and most probably the local innate immunity, which manage to modulate and finally reach the latency of the virus, which remains resident in the country [16].

The T cellular immune response is essential in defense and is of long duration. Its loss or decrease is the key to reactivation. If there is viral reactivation, a new potentiation of cellular immunity is generated (on whose effect and control capacity depends the intensity and the presence of complications).

There is also a response of specific antibodies that occurs

late and in clear relation of magnitude with the virulence of the process. In this case, the maximum level of specific antibodies is dated in the third week of evolution of HZ and has more significance as a marker of the intensity of the process (the more antibodies the more severe and prolonged the HZ, the more severe the neuralgia and the older the patient) translating more antigenic stimulus. The initial levels of specific antibodies at the onset of HZ do not correlate with the clinical course [17].

Senescence is the most common cause of loss of cellular immune protection, in addition to all pathological states of immunosuppression. Humoral immunocompetence is less important in VZV disease. Specific antibodies (hyperimmune serum) can block primoinfection, but modulation and resolution of the disease (varicella or zoster) depends on specific T-cell immunity.

Vaccines (attenuated virus) and recombinant glycoprotein E induce and potentiate immunity in the same way as virus activity, although in very elderly patients endogenous reactivation seems more potent than the vaccine [18].

In any case, if the measures of cellular immunity that we know in the laboratory are equivalent to viral reactivation and vaccines, especially the recombinant gE vaccine, and since HZ can recur, it is likely that vaccines also require booster doses, including the recombinant gE vaccine. In this case, the antigenic stimulus is punctual and does not remain latent. Its efficacy is measured and contrasted at 10 years and it seems that at that point both cell-mediated immunity (CMI) and antibody titer begin to decrease [19].

The search for vaccines against VZV has not been completed. As with other immunogens, we are looking for platforms that guarantee greater persistence of the antigenic stimulus (gE encoded in Calmette-Guérin bacilli), mRNA encodings that seem as effective as the recombinant one already in force and antigenic encodings in other vector viruses [20].

HOW IS HERPES ZOSTER DIAGNOSED? WHEN IS MICROBIOLOGICAL CONFIRMATION NECESSARY?

The clinical manifestations of HZ with skin lesions are usually so clear that in immunocompetent patients, microbiological confirmation is not required. The presence of a rash with vesicles distributed on a metamere, usually with dysesthesias or frank pain, are very characteristic.

Microbiological confirmation is necessary when the skin lesions are atypical as in the case of hemorrhagic lesions and without frank vesicles. Microbiological confirmation is also needed when there are no characteristic clinical lesions such as in patients presenting with acute neuritis (before the rash appears), atypical ocular manifestations, aseptic meningitis, myelitis, retinal necrosis, etc. Ramsay Hunt syndrome includes the triad of ipsilateral facial paralysis, otalgia and vesicles in the ear canal or pinna. It may be associated with dysgeusia, hypo- or hyperacusis, lacrimation and tongue lesions.

Laboratory confirmation is usually made on material aspirated from vesicles in the case of skin lesions or in other usually sterile fluids such as CSF. The most commonly used test today is PCR, followed by fluorescent antibody staining (direct fluorescence) and less frequently by viral isolation in cell culture.

PCR is more sensitive than the culture itself. In a study evaluating 1,479 clinical samples from 1,220 patients with suspected HZ, real-time PCR was more sensitive than culture isolation (92% vs. 53%) [21,22]. Culture, however, is necessary when sensitivity studies against antivirals are required.

WHAT HZ VACCINES ARE CURRENTLY AVAILABLE AND HOW MUCH PROTECTION DO THEY CONFER?

Currently, there are two vaccines approved by regulatory agencies and marketed to prevent the onset of HZ and its complications, essentially PHN (Table 1). They are indicated in persons over 50 years of age [20]. The first of these (Zostavax®), marketed by MSD and licensed in Europe in May 2006, is a live attenuated virus vaccine and is administered in a single dose [23-27]. It is contraindicated in states of primary or acquired immunodeficiency due to the risk of virus replication.

The second (Shingrix®) is more recent [28-33]. It was authorized in March 2018, is marketed by the company GSK and is the one that is included in the vaccination strategies by the different autonomous communities of Spain at the present time [2]. It is a recombinant vaccine containing the glycopro-

Table 1 **Immunization vaccines against Herpes zoster marketed in Spain.**

Vaccine	Characteristics	Doses	Indications
Zostavax MSD	Live attenuated viruses	1 dose 0.65 ml	Prevention of herpes zoster and post-herpetic neuralgia in adults. Post-herpetic neuralgia in adults > 50 years
Shingrix GSK	Recombinant	2 doses of 0.5 ml each, separated two months apart	Prevention of herpes zoster and postherpetic neuralgia in: - adults >50 years - adults >18 years of age at increased risk for herpes zoster

tein E of the VZV virus and the adjuvant AS01B. The latter is a compound extracted from the bark of *Quillaja saponaria*, a tree native from Chile, which has also been used in some of the SARS-CoV-2 vaccines (NVX-CoV2373 vaccine, Novavax, USA), and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) [33,34]. In the indication of the Shingrix vaccine, the age of the target population is reduced by adding the prevention of HZ and PHN in adults 18 years of age and older with immunodeficiency conditions. In all cases included in the indication for vaccination with Shingrix, administration consists of two doses of 0.5 ml each, with a minimum interval of two months between doses.

Both vaccines have a good safety profile. However, the recombinant Shingrix vaccine has greater reactogenicity, both locally and systemically. No significant differences in serious adverse effects have been demonstrated between the two vaccines. The Shingrix vaccine is more efficient and its effectiveness against HZ and subsequent neuralgia, especially in immunocompromised patients, does not decrease with age, a situation that is common with the attenuated virus vaccine (Zostavax) [35]. In addition, since it is a recombinant vaccine, virus replication is not possible, making it safe in immunocompromised patients.

Like the efficacy (derived from clinical trials), the effectiveness (assessed in real life) of vaccination with Zostavax decreases with time after vaccination. In vaccinated persons followed for at least 4 years after vaccination, the incidence of HZ ranged from 14% to 49% of that expected. When PHN was analyzed, it ranged from 45% to 62% of expected [36]. With the Shingrix vaccine, the efficacy in adults over 70 years of age was 91% for HZ and 89% for PHN, with an effectiveness of over 70% in those who had received the complete regimen. The recombinant vaccine has also been shown to be highly effective against other complications of HZ infection such as vasculitis, disseminated disease, ophthalmic disease, neurological disease, stroke and visceral disease. The efficacy of the recombinant Shingrix vaccine is not affected by underlying diseases such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, depression or chronic kidney disease and shows high efficacy in immunosuppressed individuals.

In clinical trials, Shingrix has shown superiority over the attenuated vaccine, demonstrating an elevated humoral and cellular immune response that is maintained up to 10 years after receiving the vaccine [20]. Mathematical models predict that the immune response generated after the initial vaccination with the usual two doses can be maintained for 20 or more years, so there is no consensus on the need for revaccination [19]. However, persons who have previously received the attenuated virus vaccine (Zostavax) can be vaccinated with the recombinant Shingrix vaccine [37]. The first dose with Shingrix can be administered two months after the administration of the Zostavax vaccine, although taking into account the duration of efficacy of this vaccine, it is recommended to administer the Shingrix vaccine 5 years after the previous one, and both doses should also be administered.

WHAT ARE THE INDICATIONS FOR VACCINATION AGAINST ZOSTER BY AGE CRITERIA? ARE THERE INDICATIONS TO VACCINATE IMMUNOCOMPETENT POPULATIONS OF LOW OR MIDDLE AGE?

Epidemiology alone justifies that the age criterion is one of the criteria for the indication of vaccination in the prevention of HZ and its complications [2,37]: its incidence indicates that from the age of 50 years one in five men and one in four women will suffer from HZ with a risk of suffering from it at the age of 85 years of 50%. Furthermore, by the age of 80, it is estimated that 33% of those who have suffered from HZ will develop the dreaded and disabling PHN. Hospitalization, although low, is progressively required with age: 63.1% of hospitalizations for HZ and 83.2% for PHN are in patients aged 60 years and older, with a maximum in those over 85 years. Finally, 97.2% of deaths from HZ, also exceptional, occur in persons over 65 years of age. Based on all these data, there is no doubt that the priority indication for vaccination in the immunocompetent population against HZ is all those over 65 years of age and especially all those over 80 years of age [2,37] .

The community of Madrid [37] according to the doses available has indicated to vaccinate two cohorts in 2022, on the one hand those over 80 years old and on the other hand those who will be 65 years old in 2022, being available privately with a medical prescription for the rest of the population ("the imperfect ethics of vaccines") [38]. The choice of the 65-year-old cohort is due to the fact that most of them will have had chickenpox without previous vaccination, thus placing them in an age of increasing risk, being a cohort older than the rest of the age groups.

In younger, immunocompetent adults, the recommendation for vaccination is not clear. However, some studies indicate some population groups with a higher risk of suffering from HZ regardless of age. These may include adults with COPD on inhaled or oral corticosteroids [39]. Similarly, they could also be recommended for adults suffering from COPD [40] associated with type 1 or type 2 diabetes mellitus [41,42]. Finally, hemodialysis patients should also be included. [43]. Other conditions such as dementia [44] o depression [45], although these factors alone increase the risk of HZ, there is no clear indication for vaccination at this time in age groups below 65 years.

WHICH IMMUNOSUPPRESSED PATIENTS SHOULD RECEIVE VACCINES AGAINST ZOSTER?

There are several arguments supporting the administration of the HZ vaccine in the immunocompromised population. Firstly, the incidence of HZ is higher in immunocompromised patients than in the general population. In a study carried out in the Valencian Community, the mean incidence rate in the immunocompromised population was 9.15 cases per 1,000 people in the population with different immunosuppressive diseases, compared to 4.64 cases in the general popu-

lation, reaching figures of 56 cases per 1,000 patients in those undergoing hematopoietic stem cell transplantation [46].

In addition, immunocompromised patients are at higher risk of HZ complications and more severe disease (viremia, pneumonitis, hepatitis, meningoencephalitis) than immunocompetent patients [47,48]. PHN is the most frequent complication in immunocompromised patients, with the highest rate, again, in patients undergoing hematopoietic stem cell transplantation [46]. Finally, immunocompromised patients are more likely to suffer from recurrent HZ than immunocompetent patients [49].

Immunocompromised patients were excluded from pivotal studies with HZ vaccines. Later, studies have been conducted to assess the efficacy, immunogenicity and safety of the vaccine in certain groups of immunocompromised patients (autologous hematopoietic stem cell transplantation (TaPH), hematological malignancies during immunosuppressive chemotherapy, renal transplantation, solid tumor during immunosuppressive chemotherapy and HIV infection. In TaPH recipient patients, a 68% and 89% reduction in the incidence of HZ and PHN was demonstrated, respectively, with an adverse effect rate similar to that of placebo [50]. In patients with hematologic malignancies, the vaccine achieved an 87% reduction in the incidence of HZ vs. placebo [51]. In the case of patients with solid tumors undergoing chemotherapy, with renal transplantation or HIV infection, it was shown that humoral and protective cellular immunity were achieved in very high percentages of patients, similar to those found in similar population groups without immunocompromising conditions [52-54], although no efficacy data were obtained. In all cases, the vaccine showed an acceptable safety profile.

Based on all these data, vaccination with the HZ vaccine is recommended in most countries for adult patients with various diseases that cause immunosuppression and, therefore, a much higher risk of developing the disease than the general population. Among the most frequent indications, based on the data presented, the vaccine is recommended for people with solid organ transplants, patients with HSCT, patients with solid tumors receiving chemotherapy and in patients with HIV infection, in addition to other comorbidities that may result from the disease itself or its treatment in immunodeficiency.

WHAT ARE THE MOST APPROPRIATE VACCINATION RECOMMENDATIONS? AND WHAT ARE THE CONTRAINDICATIONS OF ZOSTER VACCINES?

The recommended guidelines for vaccination against HZ are included in a document issued by the Spanish Ministry of Health [2]:

- Zostavax vaccine is administered in a single dose. It is contraindicated in immunosuppressed patients as it is a live virus vaccine. It is not indicated in patients under 50 years of age [2,55] and can be applied in people who have previously suffered from HZ, after recovery from acute HZ.
- The Shingrix vaccine is administered in a two-dose schedule, with a minimum interval of two months between doses [33]. The second dose can be administered 2 to 6 months after the first one. This vaccine is recombinant, so it is not contraindicated in immunocompromised patients, and it can also be used in adults from 18 years of age, with a high risk of suffering HZ.
- People with special risk conditions for HZ can be vaccinated with Shingrix from 18 years of age onwards, respecting the following vaccination guidelines according to the patient's underlying pathology:
  - Hematopoietic stem cell transplantation (HSCT). Vaccination from 18 years of age. Two doses will be administered, with an interval of two months. In persons who are vaccinated in the immediate post-transplant period, the first dose should be administered 2 months after transplantation.
  - Solid organ transplantation (SOT). Vaccination from 18 years of age. Two doses will be administered two months apart. If vaccinated after transplantation, the first dose of vaccine will be administered 4-8 months after transplantation.
  - Treatment with anti-JKA drugs. Vaccination from 18 years of age. Two doses will be administered two months apart, if possible vaccination should be given before starting treatment.
  - HIV-infected persons. Vaccination will be carried out in stable persons who have been on antiretroviral treatment for at least one year. Two doses will be administered with an interval of two months.
  - Hematological malignancies. Two doses will be administered, with an interval of two months. In persons who are going to start chemotherapy treatment, the first dose of vaccine should be administered at least 10 days before starting the first cycle of treatment.
  - Solid tumors undergoing chemotherapy. Two doses will be administered, with an interval of two months. The first dose can be administered after completion of chemotherapy, or in window periods without active antitumor treatment.
- Other situations to consider are those individuals previously vaccinated with Zostavax, and those who have a history of HZ, or repeated HZ, prior to vaccination:
  - Individuals who have previously received Zostavax vaccine may be revaccinated with recombinant vaccine, respecting an interval of at least 5 years between this vaccine and the first dose of Shingrix.
  - Regarding patients who have suffered HZ prior to vaccination, there are data from a clinical trial showing that the Zostavax vaccine is immunogenic and well tolerated in patients who have previously undergone HZ [56]. The safety of the HZ/su vaccine in people who have suffered a previous episode of HZ,

before being vaccinated, is not questioned, although there are no specific studies on the subject [57].

Specific contraindications for these vaccines affect only Zostavax, which is contraindicated in immunocompromised patients and in those under 50 years of age. There are no contraindications for the Shingrix vaccine.

Both vaccines are safe. Although HZ/su is associated with greater local and systemic reactogenicity compared to the ZVL vaccine, no significant differences have been demonstrated between the two vaccines in the detection of serious adverse effects, nor when compared to the placebo group [58].

CAN THE ZOSTER VACCINE BE COMBINED WITH OTHER VACCINES?

Among the interactions described in the Shingrix technical data sheet, it is specified that it can be administered concomitantly with the inactivated non-adjuvanted vaccine against seasonal influenza, with the 23-valent polysaccharide (PPV23) and 13-valent pneumococcal vaccines or with the reduced antigenic content (dTpa) diphtheria, tetanus and anti-Tetanus and Pertussis vaccine (acellular component). Caution should be taken to administer them at different injection sites. In three phase III clinical trials randomized adults ≥ 50 years of age received 2 doses of Shingrix 2 months apart, administering the first dose concomitantly or not concomitantly with an inactivated seasonal influenza vaccine, with a PPV23 vaccine, or with a dTpa vaccine, immune responses to the co-administered vaccines were not affected [59-62]. Adverse reactions, fever and chills were more frequent when Shingrix was co-administered with PPV23.

In the absence of precise data, concomitant use of the HZ vaccine with the COVID vaccine is not recommended but could be scheduled one month apart.

After the COVID-19 pandemic, it seems necessary to create a global system that can support both routine immunization and epidemic immunization in adults [59,60].

New strategies are being advanced to address the context of immunosenescence, which can reduce the efficacy of vaccines and affect susceptibility to new infections in older adults [61]. High-dose, adjuvanted and recombinant specific influenza vaccines, pneumococcal conjugate vaccines and a recombinant adjuvanted HZ vaccine have demonstrated increased efficacy and effectiveness in older adults [62,63]. Many studies have shown that vaccines against influenza, pneumococcus and HZ [64,65-68] are cost-effective when administered to older adults in a variety of settings.

WHAT IS THE BEST TREATMENT FOR ACUTE ZOSTER?

The main goals of HZ treatment are to reduce the extent and duration of skin lesions, the intensity and duration of acute pain and the incidence of PHN. In immunocompromised and other vulnerable patients, treatment aims to reduce the

Table 2 | **Indications for antivirals in acute herpes zoster infection**

a) Situations in which treatment with oral antiviral drugs is recommended
- HZ with any location in persons ≥ 50 years*.
- HZ of non-truncular involvement, in areas of the head and/or neck that seat on any cranial nerve (ophthalmic, otic or other cranial nerves), in the extremities or perineum.
- HZ at any location with:
  - Moderate to severe HZ pain
  - Hemorrhagic or necrotic lesions
  - Affection of more than one dermatome
  - Atypical/satellite vesicles
  - Mucous membrane involvement
- HZ in immunocompromised patients.
- HZ in patients with predisposing skin diseases (e.g., atopic dermatitis).
- HZ in children and adolescents with prolonged treatment with salicylic acid or corticosteroids.

b) Situations in which treatment with intravenous acyclovir is recommended
- HZ in head and/or neck areas, especially in very elderly patients.
- HZ with hemorrhagic/necrotic lesions, with involvement of more than one dermatome, with atypical/satellite vesicles, with mucosal involvement or generalized HZ.
- HZ in immunocompromised patients
- HZ with signs of visceral or CNS involvement (stepwise dose increase up to 15 mg/kg b.w., three times daily, for up to 21 days)
- Acute retinal necrosis (complication of ocular herpes): induction with IV acyclovir for 7-10 days, followed by oral acyclovir (3-4 months), and topical and systemic treatment with corticosteroids.

Modified from references 1, 2

***Initiate within 72 hours after rash onset, but may be considered for patients presenting more than 72 hours after rash onset when there are skin, motor, neurological or ocular complications or in patients with advanced age or severe pain**

Table 3 Recommended drugs for antiviral treatment of herpes zoster.

Drug	Dosage, frequency of administration and duration*
Valaciclovir (PO)	1000 mg, tid x 7 days
Aciclovir (PO)**	800 mg. 5 times/day x 7 days
Aciclovir (IV)	8–10 mg/kg, tid x 7-10 days
Famciclovir (VO)	250 mg, tid x 7 days
Brivudine (VO)	125 mg, qd x 7 days
Topical antiviral therapy is not recommended.	

Modified from reference 2

* Patients with recurrent shingles should receive antiviral treatment at a dose and duration similar to the treatment of their initial episode.

** Acyclovir and its analogues depend on renal function for their elimination and dose adjustment is necessary in case of moderate to severe renal insufficiency.

frequency and severity of complications [69]. In the absence of risk factors for the development of complications, HZ is usually a self-limited disease that does not require specific antiviral treatment. The different clinical practice guidelines agree on the indications for antiviral treatment in immunocompetent persons ≥ 50 years of age [69,70]. In addition, it would be indicated regardless of age, in cases of non-truncular involvement (such as HZ affecting the neck, extremities or perineum), in immunosuppressed patients, in cases of moderate or severe pain, in the presence of a non-mild skin rash or in patients with skin disease predisposing to complications (Table 2) [69].

Currently, there are four orally effective nucleoside analogues against HZ (Table 3) [70]. Antiviral drugs accelerate the resolution of acute HZ-related pain and may reduce the duration of the rash, but have not been shown to decrease the incidence of PHN [71]. Nor have statistically significant differences in pain cessation and resolution of skin symptoms been observed in different studies among the different antivirals [72].

Acute pain associated with HZ occurs in more than 95% of patients over 50 years of age [71]. Initially, this pain is nociceptive, but later a neuropathic component may appear. The treatment of acute pain depends on its severity and impact. Mild to moderate pain is treated with systemic analgesics. The application of cold, wet compresses over the blisters may help relieve pain. Severe cases may require opioids [70]. In the absence of acute pain control, and when a neuropathic component is suspected, analgesics can be combined with anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, venlafaxine or duloxetine as a second-line treatment [69]. It is unusual to have to resort to interventional treatments for acute pain. In relation to ocular herpes, it is recommended to complement systemic treatment with the application of topical acyclovir preparations to the affected eye [69,70]. Otic HZ has no specific topical treatment. For antiviral treatment of Bell's palsy associated with HZ, famciclovir has the best rate of recovery of facial function [73].

There is insufficient evidence and expert agreement to make recommendations for specific topical treatment of acute HZ [69]. It is advisable to keep the lesions clean and dry, avoiding as much as possible any topical treatment [69].

WHAT IS THE MANAGEMENT OF MEDIUM AND LONG-TERM COMPLICATIONS: POSTHERPETIC NEURALGIA?

PHN is the most common complication of HZ infection. It is defined as neuropathic pain that persists 30 to 90 days after the cutaneous flare. It is characterized by continuous or paroxysmal, evoked or spontaneous, burning, and lacerating pain. It is associated with dysesthesias, paresthesias, hyperalgesia, hyperesthesia and allodynia. Pain usually alters the patient's quality of life and can lead to functional limitation, social isolation and psychological disorders. The most frequent clinical form is intercostal, affecting one or two pairs of intercostal roots and ganglia on one side. The most frequent lesion of the cranial nerves is in the trigeminal nerve, giving rise to ophthalmic HZ, which is accompanied by pain in 93% of patients.

Between 5-20% of patients with HZ will present PHN [73]. Its appearance is related to age, being more frequent after 50 years of age, the extension of the skin lesion and the intensity of the prodromal pain [74]. Other related factors are ophthalmic involvement, immunosuppression, the presence of other diseases such as diabetes or delayed initiation of herpes treatment.

Its pathogenesis has not been completely clarified. Histologically, alterations have been found in both the central and peripheral nervous system, with inflammation and necrosis from the peripheral nerve to the neurons of posterior medullary cords. There also appears to be demyelination with loss of inhibitory stimulus for nociceptive afferents in the spinal cord. There is sensitization of peripheral nociceptors with reduction of the excitation threshold; appearance of spontaneous ectop-

ic discharges in peripheral and central axons, medullary hyperexcitability and loss of inhibitory control of pain. An alteration of sodium channels has also been considered in this disease and the expression of neuronal genes after infection.

The management of PHN is based on prevention through vaccination in the population at risk, early administration of antivirals upon HZ infection and symptomatic control by individualized multimodal medication regimens and invasive procedures.

The only preventive measure at present is vaccination. Different studies have shown that vaccination with attenuated and recombinant virus reduces the occurrence of HZ zoster in the following 3 years [9,75], it reduces also the incidence of PHN, as well as the hospital admissions related to the disease [32,76].

As mentioned in the previous section, the use of antivirals (acyclovir, brivudine, valacyclovir and famciclovir) is recommended in patients over 50 years of age early in the acute phase, although there is no convincing evidence that antiviral treatment reduces PHN [71]. Nor have corticosteroids shown clear evidence of benefit [13,77].

The most commonly used treatments for the control of PHN are tricyclic antidepressants, gabapentin, pregabalin and, locally, lidocaine and capsaicin patches. Other drugs such as antiepileptics (valproic acid, carbamazepine, lamotrigine) and serotonin reuptake inhibitors have been used in refractory cases. Opioid analgesics have shown efficacy in PHN. Invasive therapies include botulinum toxin injections, sympathetic blockade with local anesthetics, epidural/intrathecal steroid injections and spinal cord stimulation [78] but the tolerability and safety of these procedures must be considered [79]. Finally, cognitive and behavioral therapies can improve the quality of life of these patients.

WHAT IS THE POSITION OF THE DIFFERENT HEALTH ADMINISTRATIONS IN SPAIN REGARDING VACCINES AGAINST ZOSTER?

In March 2021, a document of recommendations, drawn up by consensus at the Interterritorial Council of the Ministry of Health in Spain, is published [2]. In this document, the following vaccination recommendations are established, which would be mandatory in all Autonomous Communities:

- Population over 18 years of age with the following risk factors: hematopoietic progenitor transplantation, solid organ transplantation, treatment with anti-JKA drugs, HIV infection, hematological malignancies and solid tumors undergoing chemotherapy.
- General population over 65 years of age.

Based on this document, several limitations can be pointed out: the age of recommendation, the demographic choice of the cohorts and, finally, something inherent to the system, the lack of homogeneity in the application of the recommendations by the communities.

Firstly, it is not sufficiently explained why the indication in the general population is established at 65 years of age and not at 50 years of age, which is when the dramatic inflection in the HZ growth curve occurs. In fact, the CDC recommends vaccination against HZ for all immunocompetent adults over 50 years of age, whether or not they have had a previous episode of HZ and whether or not they have received previous vaccination against varicella (chickenpox) [80].

On the other hand, the aforementioned document states that an attempt will be made to vaccinate one or two age cohorts each year, starting with those who turn 65 and/or 80 years of age in the year in which the procedure is performed. Since the document states that vaccination in immunocompetents will be implemented based on availability, it seems clear that both the age threshold and the surprisingly odd selection of cohorts is determined by economic and logistical reasons of human resources and infrastructure. It is possible, assuming that vaccination will be carried out with two doses, but on a single basis, that this choice would allow vaccination to be completed in 6-8 years.

As for the application by the communities, it could be assumed that all would apply the recommendations uniformly, but the reality is that at least the times are different and even with regard to vaccination in immunocompromised patients, Andalusia only carries it out in those undergoing hematopoi-

Table 4 Status of Herpes Zoster vaccination in the Autonomous Communities

Territory	PLAN	GR Status	State Population >65
Andalusia	2021	Group I	¿?
Aragon	2021	All	Expected 2023
Asturias	2021	All	Yes
Balearic Islands	2021	All	Planned 2023
Canary Islands	2021	All	¿?
Cantabria	2021	All	Planned 2023
Castilla Mancha	2021	All	Planned 2023
Castilla Leon	2021	All	Planned 2023
Catalonia	2021	All	Yes
Extremadura	2021	All	¿?
Galicia	2021	All	¿?
La Rioja	2021	All	¿?
Madrid	2021	All	Yes
Murcia	2021	All	Planned 2023
Navarra	2021	All	¿?
Basque Country	2021	All	¿?
Valencia	2021	All	Planned 2023
Ceuta	2021	All	Planned 2023
Melilla	2021	All	Planned 2023

etic progenitor transplantation. It is not easy to know the exact situation in which they find themselves, nor even to know the availability of doses. Madrid purchased 250,000 doses of vaccine starting to vaccinate immunocompromised patients last January and the general population over 65 years of age in May 2022. With the information that can be obtained at the end of November 2022, only three communities, Madrid, Catalonia and Asturias applied the vaccination to both immunocompromised and immunocompetent patients, the latter following the recommendation of 65 and 80 years of age, although 6 more communities and the cities of Ceuta and Melilla have announced that they will do so during 2023 (Table 4).

In this situation, some doubts arise that it would be advisable for the administration to clear up. The first concerns the selection of cohorts. Assuming that it is over 65 years of age, there is no justification for choosing 2 extreme cohorts that will leave out, for years, population groups aged 70-75 years in which the incidence is very high. On the other hand, and partly as a consequence of this situation, since it is a vaccine that can be purchased on prescription at the pharmacy, although it is not financed by the SNS and is expensive, since the necessary doses exceed 400€, it is clear that the application of this rule could result in a loss of equity, since the population with greater purchasing power, not only over 65 but even over 50 years of age, could have access to the vaccine, something difficult for the most disadvantaged groups. Finally, up to now the dissemination to the population and health personnel is scarce, so that it is possible that vaccination is not being carried out as planned, even in the general population groups chosen. Vaccinating in nursing homes or systematically taking advantage of consultations with the elderly population would increase the number of vaccinated subjects and would make it possible to take stock of the management of doses and increase the population cohorts to be vaccinated (Table 4).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015;3(4):109-20. 10.1177/2051013615599151 PMC4591524
2. Ministerio de Sanidad, Herpes Zoster: Recomendaciones Vacunacion. 2021. Available at: https://www.sanidad.gob.es/en/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/docs/HerpesZoster_RecomendacionesVacunacion.pdf
3. Instituto de Salud Carlos III. Informes Anuales de la Red Nacional de Vigilancia Epidemiológica (RENAVE). Resultados de la vigilancia epidemiológica de las enfermedades transmisibles. informe anual. años 2017-2018. 2018. Available at: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/INFORMES%20RENAVE/RENAVE_Informe_anual__2017-2018.pdf
4. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014;4(6):e004833. 10.1136/bmjopen-2014-004833 PMC4067812
5. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, et al. Varicella zoster virus infection. Nat Rev Dis Primers. 2015;1:15016. 10.1038/nrdp.2015.16 PMC5381807
6. Hope-Simpson RE. THE NATURE OF HERPES ZOSTER: A LONG-TERM STUDY AND A NEW HYPOTHESIS. Proc R Soc Med. 1965;58(1):9-20. PMC1898279
7. Centers for Disease Control. Evolution of varicella surveillance--selected states, 2000-2010. MMWR Morb Mortal Wkly Rep. 2012;61(32):609-12.
8. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet. 1974;2(7892):1288-90. 10.1016/s0140-6736(74)90144-5
9. Harpaz R. Do varicella vaccination programs change the epidemiology of herpes zoster? A comprehensive review, with focus on the United States. Expert Rev Vaccines. 2019;18(8):793-811. 10.1080/14760584.2019.1646129
10. Laing KJ, Ouwendijk WJD, Koelle DM, Verjans G. Immunobiology of Varicella-Zoster Virus Infection. J Infect Dis. 2018;218(suppl_2):S68-s74. 10.1093/infdis/jiy403 PMC6151075
11. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. Stroke. 2009;40(11):3443-8. 10.1161/strokeaha.109.562017
12. Franco-Paredes C, Bellehemeur T, Merchant A, Sanghi P, DiazGranados C, Rimland D. Aseptic meningitis and optic neuritis preceding varicella-zoster progressive outer retinal necrosis in a patient with AIDS. Aids. 2002;16(7):1045-9. 10.1097/00002030-200205030-00011
13. Ku CC, Padilla JA, Grose C, Butcher EC, Arvin AM. Tropism of varicella-zoster virus for human tonsillar CD4(+) T lymphocytes that express activation, memory, and skin homing markers. J Virol. 2002;76(22):11425-33. 10.1128/jvi.76.22.11425-11433.2002 PMC136789
14. Levin MJ. Varicella-zoster virus and virus DNA in the blood and oropharynx of people with latent or active varicella-zoster virus infections. J Clin Virol. 2014;61(4):487-95. 10.1016/j.jcv.2014.09.012
15. Abendroth A, Kinchington PR, Slobedman B. Varicella zoster virus immune evasion strategies. Curr Top Microbiol Immunol. 2010;342:155-71. 10.1007/82_2010_41 PMC3936337
16. Kennedy PG, Grinfeld E, Gow JW. Latent varicella-zoster virus is located predominantly in neurons in human trigeminal ganglia. Proc Natl Acad Sci U S A. 1998;95(8):4658-62. 10.1073/pnas.95.8.4658 PMC22546
17. Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR,

Caulfield MJ, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis. 2009;200(7):1068-77. 10.1086/605611 PMC4014851

18. Schwarz TF, Volpe S, Catteau G, Chlibek R, David MP, Richardus JH, et al. Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccin Immunother. 2018;14(6):1370-7. 10.1080/21645515.2018.1442162 PMC6037441
19. Hastie A, Catteau G, Enemuo A, Mrkvan T, Salaun B, Volpe S, et al. Immunogenicity of the Adjuvanted Recombinant Zoster Vaccine: Persistence and Anamnestic Response to Additional Doses Administered 10 Years After Primary Vaccination. J Infect Dis. 2021;224(12):2025-34. 10.1093/infdis/jiaa300 PMC8672743
20. Harbecke R, Cohen JI, Oxman MN. Herpes Zoster Vaccines. J Infect Dis. 2021;224(12 Suppl 2):S429-s42. 10.1093/infdis/jiab387 PMC8482024
21. Harbecke R, Oxman MN, Arnold BA, Ip C, Johnson GR, Levin MJ, et al. A real-time PCR assay to identify and discriminate among wild-type and vaccine strains of varicella-zoster virus and herpes simplex virus in clinical specimens, and comparison with the clinical diagnoses. J Med Virol 2009;81 1310.
22. Kino Y, Minamishima Y. Diagnosis of zoster and evaluation of varicella vaccine with a passive haemagglutination assay. Vaccine. 1993;11(11):1151-3. 10.1016/0264-410x(93)90078-c
23. Herpes zoster vaccine (Zostavax). Med Lett Drugs Ther. 2006;48(1243):73-4.
24. Holcomb K, Weinberg JM. A novel vaccine (Zostavax) to prevent herpes zoster and postherpetic neuralgia. J Drugs Dermatol. 2006;5(9):863-6.
25. Ebede TL, Zippin JH. Varicella virus and the herpes zoster vaccine. A review of Zostavax and the new AFIP recommendations. J Drugs Dermatol. 2008;7(12):1173-6.
26. Holcomb K, Weinberg JM. A novel vaccine (Zostavax) to prevent herpes zoster. G Ital Dermatol Venereol. 2008;143(2):119-23.
27. Herpes zoster vaccine (Zostavax) revisited. Med Lett Drugs Ther. 2010;52(1339):41.
28. Shingrix--an adjuvanted, recombinant herpes zoster vaccine. Med Lett Drugs Ther. 2017;59(1535):195-6.
29. Bharucha T, Ming D, Breuer J. A critical appraisal of 'Shingrix', a novel herpes zoster subunit vaccine (HZ/Su or GSK1437173A) for varicella zoster virus. Hum Vaccin Immunother. 2017;13(8):1789-97. 10.1080/21645515.2017.1317410 PMC5557227
30. Deshpande L. Recombinant Zoster Vaccine (Shingrix) for the Prevention of Shingles. Am Fam Physician. 2018;98(8):539-40.
31. Maltz F, Fidler B. Shingrix: A New Herpes Zoster Vaccine. P t. 2019;44(7):406-33. PMC6590925 this article.
32. Izurieta HS, Wu X, Forshee R, Lu Y, Sung HM, Agger PE, et al. Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. Clin Infect Dis. 2021;73(6):941-8. 10.1093/cid/ciab125
33. GSK. Data sheet Shingrix. 2017. Available at: https://cima.aemps.es/cima/pdfs/es/ft/1181272001/FT_1181272001.pdf
34. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. . N Engl J Med 2020;(383(24)):2320-32. 10.1056/NEJMoa2026920.
35. López-Fauqued M, Campora L, Delannois F, El Idrissi M, Oostvogels L, De Looze FJ, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-93. 10.1016/j.vaccine.2019.03.043
36. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med. 2013;10(4):e1001420. 10.1371/journal.pmed.1001420 PMC3621740 monitoring boards for Abbott and Astellas. The authors declare no other conflicts of interest.
37. Comunidad de Madrid. Inclusión de la vacuna frente a herpes zoster (HZ) en el calendario sistemático de vacunación. Información para profesionales sanitarios. 2022. Available at: https://www.comunidad.madrid/servicios/salud/vacunas-informacion-profesionales.
38. Urioste R. La ética imperfecta de las vacunas. . Redacción Médica 2021 Available at: https://www.redaccionmedica.com/opinion/ramiro-urioste-5933/la-etica-imperfecta-de-las-vacunas-8009
39. Yang YW, Chen YH, Wang KH, Wang CY, Lin HW. Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. Cmaj. 2011;183(5):E275-80. 10.1503/cmaj.101137 PMC3060212
40. Muñoz-Quiles C, López-Lacort M, Díez-Domingo J. Risk and impact of herpes zoster among COPD patients: a population-based study, 2009-2014. BMC Infect Dis. 2018;18(1):203. 10.1186/s12879-018-3121-x PMC5934818
41. Lai SW, Liu CS, Kuo YH, Lin CL, Hwang BF, Liao KF. The incidence of herpes zoster in patients with diabetes mellitus: A meta-analysis of cohort studies. Medicine (Baltimore). 2021;100(16):e25292. 10.1097/md.0000000000025292 PMC8078473
42. Saadatian-Elahi M, Bauduceau B, Del-Signore C, Vanhems P. Diabetes as a risk factor for herpes zoster in adults: A synthetic literature review. Diabetes Res Clin Pract. 2020;159:107983. 10.1016/j.diabres.2019.107983
43. Kuo CC, Lee CT, Lee IM, Ho SC, Yang CY. Risk of herpes zoster in patients treated with long-term hemodialysis: a matched cohort study. Am J Kidney Dis. 2012;59(3):428-33. 10.1053/j.ajkd.2011.10.049
44. Chen VC, Wu SI, Huang KY, Yang YH, Kuo TY, Liang HY, et al. Herpes Zoster and Dementia: A Nationwide Population-Based Cohort Study. J Clin Psychiatry. 2018;79(1). 10.4088/JCP.16m11312
45. Liao CH, Chang CS, Muo CH, Kao CH. High prevalence of herpes zoster in patients with depression. J Clin Psychiatry. 2015;76(9):e1099-104. 10.4088/JCP.14m09311
46. Muñoz-Quiles C, López-Lacort M, Díez-Domingo J, Orrico-Sánchez A. Herpes zoster risk and burden of disease in immunocompromised populations: a population-based study using health system integrated databases, 2009-2014. BMC Infect Dis. 2020;20(1):905. 10.1186/s12879-020-05648-6 PMC7708196

47. Kennedy PGE, Gershon AA. Clinical Features of Varicella-Zoster Virus Infection. Viruses. 2018;10(11). 10.3390/v10110609 PMC6266119

48. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-26. 10.1086/510206

49. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc. 2011;86(2):88-93. 10.4065/mcp.2010.0618 PMC3031432

50. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, López-Jiménez J, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. Jama. 2019;322(2):123-33. 10.1001/jama.2019.9053 PMC6618796

51. Dagnew AF, Ilhan O, Lee WS, Woszczyk D, Kwak JY, Bowcock S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019;19(9):988-1000. 10.1016/s1473-3099(19)30163-x

52. Vink P, Delgado Mingorance I, Maximiano Alonso C, Rubio-Viqueira B, Jung KH, Rodriguez Moreno JF, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: A randomized trial. Cancer. 2019;125(8):1301-12. 10.1002/cncr.31909 PMC6766894

53. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, Kim SJ, Kim SI, Zaltzman J, et al. Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial. Clin Infect Dis. 2020;70(2):181-90. 10.1093/cid/ciz177 PMC6938982

54. Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015;211(8):1279-87. 10.1093/infdis/jiu606 PMC4371767

55. MSD. Data sheet Zostavax. 2006. Available at: https://cima.aemps.es/cima/pdfs/es/ft/06341011/FT_06341011.pdf

56. Mills R, Tyring SK, Levin MJ, Parrino J, Li X, Coll KE, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine. 2010;28(25):4204-9. 10.1016/j.vaccine.2010.04.003

57. Godeaux O, Kovac M, Shu D, Grupping K, Campora L, Douha M, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults ≥ 50 years of age with a prior history of herpes zoster: A phase III, non-randomized, open-label clinical trial. Hum Vaccin Immunother. 2017;13(5):1051-8. 10.1080/21645515.2016.1265715 PMC5443374

58. Willis ED, Woodward M, Brown E, Popmihajlov Z, Saddier P, Annunziato PW, et al. Herpes zoster vaccine live: A 10 year review of post-marketing safety experience. Vaccine. 2017;35(52):7231-9. 10.1016/j.vaccine.2017.11.013 PMC5739308

59. Privor-Dumm LA, Poland GA, Barratt J, Durrheim DN, Deloria Knoll M, Vasudevan P, et al. A global agenda for older adult immunization in the COVID-19 era: A roadmap for action. Vaccine. 2021;39(37):5240-50. 10.1016/j.vaccine.2020.06.082 PMC7332930

60. Bouza E, Ancochea-Bermúdez J, Campins M, Eirós-Bouza JM, Fargas J, García Rojas A, et al. The situation of vaccines for the prevention of infections in adults: An opinion paper on the situation in Spain. Rev Esp Quimioter. 2019;32(4):333-64. PMC6719651

61. Thomas-Crusells J, McElhaney JE, Aguado MT. Report of the ad-hoc consultation on aging and immunization for a future WHO research agenda on life-course immunization. Vaccine. 2012;30(42):6007-12. 10.1016/j.vaccine.2012.07.025

62. Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines. 2018;17(5):435-43. 10.1080/14760584.2018.1471989

63. McElhaney JE, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis. 2013;13(6):485-96. 10.1016/s1473-3099(13)70046-x

64. Ting EEK, Sander B, Ungar WJ. Systematic review of the cost-effectiveness of influenza immunization programs. Vaccine. 2017;35(15):1828-43. 10.1016/j.vaccine.2017.02.044

65. Chen C, Beutels P, Wood J, Menzies R, MacIntyre CR, McIntyre P, et al. Retrospective cost-effectiveness of the 23-valent pneumococcal polysaccharide vaccination program in Australia. Vaccine. 2018;36(42):6307-13. 10.1016/j.vaccine.2018.08.084

66. Jiang Y, Yang X, Taniguchi K, Petigara T, Abe M. A cost-effectiveness analysis of revaccination and catch-up strategies with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in older adults in Japan. J Med Econ. 2018;21(7):687-97. 10.1080/13696998.2018.1465272

67. Thorrington D, van Rossum L, Knol M, de Melker H, Rümke H, Hak E, et al. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018;13(2):e0192640. 10.1371/journal.pone.0192640 PMC5806887

68. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018;14(5):1218-29. 10.1080/21645515.2018.1428507 PMC5989887

69. Werner RN, Nikkels AF, MarinovićB, Schäfer M, Czarnecka-Operacz M, Agius AM, et al. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. J Eur Acad Dermatol Venereol. 2017;31(1):20-9. 10.1111/jdv.13957

70. Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. Am Fam Physician. 2017;96(10):656-63.

71. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2014(2):Cd006866. 10.1002/14651858.CD006866.pub3

72. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. Arch Fam Med. 2000;9(9):863-9. 10.1001/archfami.9.9.863

73. Cao J, Zhang X, Wang Z. Effectiveness comparisons of antiviral treatments for Bell palsy: a systematic review and network meta-analysis. J Neurol. 2022;269(3):1353-67. 10.1007/s00415-021-10487-9

74. Zhou H, Wang Z, Jin H, Chen X, Lei L. A systematic review and meta-analysis of independent risk factors for postherpetic neuralgia. Ann Palliat Med. 2021;10(12):12181-9. 10.21037/apm-21-3028

75. Gagliardi AM, Andriolo BN, Torloni MR, Soares BG, de Oliveira Gomes J, Andriolo RB, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev. 2019;2019(11). 10.1002/14651858.CD008858.pub4 PMC6836378 none known Bernardo GO Soares: none known Juliana O Gomes: none known Regis B Andriolo: none known Eduardo C Cruz: none known

76. Lee C, Jiang N, Tang H, Ye C, Yuan Y, Curran D. Potential public health impact of the adjuvanted recombinant zoster vaccine among people aged 50 years and older in Beijing. Hum Vaccin Immunother. 2021;17(10):3735-46. 10.1080/21645515.2021.1932216 PMC8437530

77. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2013(3):Cd005582. 10.1002/14651858.CD005582.pub4

78. Patil A, Goldust M, Wollina U. Herpes zoster: A Review of Clinical Manifestations and Management. Viruses. 2022;14(2). 10.3390/v14020192 PMC8876683

79. Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc. 2016;9:447-54. 10.2147/jmdh.S106340 PMC5036669

80. Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018;67(3):103-8. 10.15585/mmwr.mm6703a5 PMC5812314

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Review

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Recommendations on the use of azole antifungals in hematology-oncology patients

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ABSTRACT

The administration of antifungals for therapeutic and, especially, prophylactic purposes is virtually a constant in patients requiring hematology-oncology treatment. Any attempt to prevent or treat *Aspergillus* or *Mucor* infections requires the administration of some drugs in the azole group, which include voriconazole, posaconazole and isavuconazole, noted for their activity against these pathogens. One very relevant aspect is the potential risk of interaction when associated with one of the antineoplastic drugs used to treat hematologic tumors, with serious complications. In this regard, acalabrutinib, bortezomib, bosutinib, carfilzomib, cyclophosphamide, cyclosporine A, dasatinib, duvelisib, gilteritinib, glasdegib, ibrutinib, imatinib, nilotinib, ponatinib, prednisone, ruxolitinib, tacrolimus, all-transretinoic acid, arsenic trioxide, venetoclax, or any of the vinca alkaloids, are very clear examples of risk, in some cases because their clearance is reduced and in others because of increased risk of QTc prolongation, which is particularly evident when the drug of choice is voriconazole or posaconazole.

Keywords: Azoles, hematology patients, drug-drug interactions

Recomendaciones sobre el uso de antifúgicos azolicos en el paciente oncohematológico

RESUMEN

La administración de antifúngicos con fines terapéuticos y especialmente, profilácticos es casi un constante en el paciente que precisa tratamiento oncohematológico. El intento de evitar o de tratar infecciones por *Aspergillus* o por *Mucor* exige la administración de algunos fármacos pertenecientes al grupo de los azoles, entre los que destacan por su actividad frente a estos patógenos, voriconazol, posaconazol e isavuconazol. Un aspecto de gran importancia es el riesgo potencial de interacciones cuando se asocian a alguno de los fármacos antineoplásico utilizados en el tratamiento de los tumores hematológicos, dando lugar a graves complicaciones. En este sentido, acalabrutinib, bortezomid, bosutinib, carfizolid, ciclofosfamida, ciscloporina A, dasatinib, duvelisib, gilteritinib, glasdegib, ibrutinib, imatinib, nilotinib, ponatinib, prednisona, ruxolitinib, tacrolimus, trans-

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retinoico, trióxido de Arsenio, venetoclax, o cualquiera de los alcaloides de la vinca, representan ejemplos muy evidentes de riesgos en unos casos porque su aclaramiento resulta reducido, en otros porque que se potencia el riesgo de prolongación del QTc, especialmente evidentes cuando el fármaco elegido es voriconazol o posaconazol.

Palabras clave: Azoles, pacientes hematológicos, interacciones medicamentosas

PREAMBLE

The reduction in patient immunity resulting from the use of increasingly effective drugs in the treatment of serious diseases has led, inter alia, to an increase in the frequency and severity of invasive fungal infections. This circumstance is common in oncology patients, among whom hematology-oncology patients are a very special population as they commonly present with long-lasting neutropenia [1-5] Some genera of fungi are especially frequent in the genesis of invasive fungal infection. *Candida*, *Aspergillus*, *Scedosporium*, *Fusarium* and *Mucorales* are notable examples of pathogens with high mortality, both in general and in this type of patients: *Candida* exceeds 10% while the remaining pathogens, including *Aspergillus*, can exceed 50%. Given this characteristic, the use of antifungals with activity against this type of pathogens is essential for both the prophylaxis and treatment of this type of infectious disease.

Since their spectrum encompasses most of the above pathogens, and *Aspergillus* in particular, the azoles (itraconazole, voriconazole, posaconazole and isavuconazole) are the most notable antifungals used in this indication. The management of these drugs, whose most typical characteristics are detailed below, is complex in several areas, including the risk of interactions with other drugs due to the altered enzymatic activity of some CYP450 components, and also because of their capacity to prolong the QT interval. These two situations often pose a serious problem when the patient is treated with any of the more relevant hematology-oncology drugs. The authors therefore considered it appropriate to make the specific recommendations set out in this article.

CYP450 SYSTEM AND TRANSPORT PROTEINS

The origins of the pharmacokinetic interactions involving azoles lie in the capacity exhibited by these drugs to inhibit the activity of some of the CYP450 isoenzymes that also participate in their metabolism. In addition, some of the drugs are substrates of transport proteins, especially P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) which they are also capable of inhibiting. This suggests risks of interactions with other drugs that are substrates of these transport proteins. Table 1 describes the effects of the various azoles on the different CYP450 isoenzymes and transport proteins.

The CYP450 system is a group of enzymes involved in the metabolism of a large number of substrates [6], including numerous drugs, whose most constant characteristic is their low water solubility and high polarity, raising difficulties for their elimination through a water-rich medium, such as urine [7].

The diverse CYP450 isoenzymes catalyze different types of reactions in the form of oxidation, reduction or hydrolysis oxidation. These reactions require oxygen (O_2) and NADPH to oxidize the substrates through monooxidation reactions. The enzymes that catalyze this type of oxidation are called monooxygenases or mixed-function oxidases. The oxidations catalyzed by this enzyme system include: aromatic and aliphatic hydroxylations, N- and S-oxidations, epoxidations, O-, N-, and S-dealkylations, deaminations, desulfurizations, dehalogenations, and dehydrogenations.

The CYP450 system is configured into different isoenzymes that are named using a predefined system. The P450s are identified by the acronym CYP (for *cytochrome P*) followed by a number designating the family, a letter identifying the subfamily and another Arabic numeral corresponding to the gene (e.g. CYP1A1, CYP2C9).

These enzymes are found in the smooth endoplasmic reticulum of hepatocytes and jejunal intestinal epithelial cells, and are also found in the lung, brain and kidney. There are almost fifty isoenzymes in the human body, although the most numerous and, therefore, the most important, given that they are responsible for drug metabolism, are: CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19, and CYP2E1 [8]. Of these, CYP3A4 is involved in the metabolism and interactions of almost 50% of drugs [9]. In addition, this isoenzyme is present in the intestinal mucosa and is therefore responsible for the first-pass metabolism of many drugs, which can, in some cases, significantly reduce their bioavailability [7,10].

One important characteristic of CYP450 isoenzymes is

Table 1 Effects of azoles on CYP450 isoenzymes and transport proteins. (Source: prescribing information. Spanish Agency of Medicines and Medical Devices)

Itraconazole	Potent CYP3A4 inhibitor, P-gp inhibitor and breast cancer resistance protein (BCRP) inhibitor.
Voriconazole	Inhibits CYP2C19, CYP2C9 and CYP3A4 enzymes.
Posaconazole	Potent CYP3A4 inhibitor.
Isavuconazole	Moderate CYP3A4/5 inhibitor, mild CYP2B6 inducer, mild P-gp inhibitor, mild inhibitor of organic cation transporter 2 (OCT2) and UGT.

P-gp: P-glycoprotein. UGT: UDP-glucuronosyltransferase.

their broad interindividual variability in relation to various factors, including the use of xenobiotics capable of increasing or reducing their enzymatic activity that can independently affect both liver and intestinal enzymes [11]. This suggests that there may be differences in the consequences of CYP3A4-inhibition interactions depending on the oral bioavailability of the substrates. For example, the impact of the consequences will be far greater on drugs with an elevated first-pass metabolism, since the effects of increased intestinal absorption will combine with those of reduced hepatic clearance. For substrates with high oral bioavailability, the interaction will only affect metabolism, resulting in a lesser impact on the bioavailability of the drug [10]. Similarly, a drug that is administered intravenously may have an inhibitory effect on hepatic CYP3A4, while when administered orally it will produce dual inhibition of both hepatic CYP3A4 and intestinal CYP3A4.

Inductors and inhibitors of isoenzymes produce their effects in a dose/concentration dependent manner but the timing is different because, while inhibition occurs immediately, induction requires protein synthesis and therefore can take up to 2 weeks to fully manifest [7–9].

The maximum impact of the inhibition of the activity of isoenzymes on pharmacokinetics lies in the drugs that are transformed and eliminated exclusively by the isoenzyme, since it cannot be eliminated until the inhibition disappears. In other cases, the effect may be much lower because there are other drug metabolism pathways that can somehow compensate for the deficient activity of the inhibited mechanism.

Transport proteins. The proteins that transport drugs through the body also play a relevant albeit lesser-known role in the origin of certain interactions [12]. Within this group of proteins, probably the best known and most studied is P-glycoprotein (P-gp). The physiological function of these proteins is to facilitate the active transport of various substrates and xenobiotics through the body, and they participate in facilitating or impeding intestinal absorption, biliary excretion, renal excretion, blood-brain barrier access, etc [13–16].

P-gp is a membrane glycoprotein predominantly found in cells of the liver, intestinal, renal, pancreas, and adrenal glands, among others. Its basic function is to excrete drugs into the bile, intestinal lumen, and urine, preventing access to the central nervous system at the blood-brain barrier [8]. Essentially, then, it prevents access by the drug to plasma while facilitating its elimination and preventing its access to brain tissue [17].

P-gp and CYP3A4 are expressed at the same time in the small intestine and liver and therefore, they may work in association to prevent drug absorption, the former by expelling them into the intestinal lumen and the latter by transforming them into metabolites [11]. The effect of P-gp may be saturated, in which case the molecules can reach venous territory as they are not expelled into the intestinal lumen. Highly lipid-soluble molecules can diffuse rapidly in this instance.

The synergistic effect on inhibition of P-gp and CYP3A4 leads to some important differences in practice. Fluconazole mildly/moderately increases immunosuppressant bioavailability, while ketoconazole produces a very intense effect, to the extent of being partially contraindicated. The explanation lies in the latter's ability to saturate P-gp compared to the absence of effects on P-gp of fluconazole. This difference is also present in relation to the route of administration: intravenous fluconazole mildly increases tacrolimus bioavailability while, with ketoconazole administered orally, the increase is very substantial [18–21].

The factors involved in the genesis and intensity of the consequences of this type of interaction are, nonetheless, highly diverse [22,23]. Some of the most relevant include sex, age, polymorphisms, and disease [10]. Logically, the variability in the pharmacokinetic processing of the substrate or drug altering the activity of isoenzymes and transport proteins is also clearly relevant [24].

QT interval prolongation. The QT interval is the electrocardiographic representation of the action potential duration of ventricular myocytes. Prolongation of this interval may be associated with torsades de pointes (TdP) ventricular tachycardia, syncope, and sudden cardiac death (SCD). The greater the prolongation of the QT interval, the more likely TdP and SCD are, especially if it is greater than 500 ms [25].

The mechanism most frequently linked to drug-induced QT prolongation is IKr channel blockade, likely facilitated by genetic predisposition. The enzyme system responsible for drug metabolism also plays a role, as this phenomenon is often concentration dependent. The presence of high concentrations facilitates channel blockade. Hence, inhibition of CYP450 activity, especially of isoenzymes CYP3A4 and CYP2D6, is usually a determining factor. As stated earlier, a number of factors commonly converge in its genesis, such as the combination of drugs that block ion channels, the combined use of any of these drugs with inhibitors of their metabolism, the presence of long QT syndrome (LQTS), bradycardia, female sex, advanced age, hypokalemia, hypomagnesemia, hypocalcemia, left ventricular dysfunction and heart failure, and previous history [25,26].

As we will explain, the problem may lie with some azole antifungals and amphotericin B itself, through hypokalemia in this case [27], a property shared by many of the drugs used in oncology-hematology. This circumstance explains why many of these drugs have contraindications or precautions in their prescribing information that include the consideration of carefully evaluating their association with other drugs that cause QT prolongation or any of the predisposing factors. We refer readers interested in reviewing this LQTS topic in greater detail to the more specific literature [28–31].

AZOLE ANTIFUNGALS

Itraconazole. A broad-spectrum antifungal drug [32] for oral or intravenous use, usually administered twice a day at daily doses ranging from 200 to 800 mg. It has an elimination half-life of 20–30 h in relation to auto-inhibition of its metabolism [33,34], which occurs via CYP3A4.

This azole acts as a potent inhibitor of the isoenzyme that metabolizes it, since the inhibitory constant (IC_{50}) for CYP3A4 is 0.0326 µM [35]. The most important metabolite is hydroxy-itraconazole, which is also metabolized through CYP3A4 [36]. Itraconazole exhibits some inhibitory activity against CYP2C9 and 2C19, although its inhibitory potency is lower: IC_{50} of 10 µM [35]. It likewise inhibits P-gp and BCRP [37].

Given this inhibitory potential, the drug's prescribing information [37] expressly recommends using it with caution with idelalisib, bosutinib, dasatinib, ibrutinib, nilotinib and vinca alkaloids. In general, they are not recommended and should be avoided even up to 2 weeks after itraconazole withdrawal. In the event that the combination is unavoidable, careful clinical monitoring is necessary and the dose should be reduced where not essential [37].

After completion of treatment, plasma concentrations of itraconazole decrease to a nearly undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with liver cirrhosis or in patients receiving CYP3A4 inhibitors, the decrease in plasma concentrations may be even more gradual. This is especially important when starting treatment with drugs whose metabolism is affected by itraconazole [37].

Itraconazole has been associated with QT interval prolongation and during interactions due to inhibition of the metabolism of other drugs, and with torsades de pointes [38-41]. Concomitant administration with CYP3A4 substrates that also prolong QT is contraindicated as it may result in elevated plasma concentrations, which may lead to increased or prolonged pharmacological effects, including adverse reactions, to such an extent that a potentially serious situation may arise.

Voriconazole. Voriconazole is one of the broad-spectrum azoles exhibiting *in vitro* activity against *Aspergillus*, *Candida*, *Scedosporium*, and some *Fusarium* species [42]. It has good oral bioavailability and sequential IV/PO therapy is possible. It is used in initial loading doses: 400 mg/12 h orally (PO) and 6 mg/kg every 12 h intravenously (IV). The maintenance dose is 200 mg/12 h and 4 mg/kg/12 h, PO/IV, respectively [43]. It produces auto-inhibition of its metabolism so the pharmacokinetics are not linear, since it undergoes a disproportionate increase in the area under the curve (AUC) and maximum plasma concentration (C_{max}) over time [44,45]. Voriconazole is metabolized through CYP2C19, with CYP3A4 and CYP2C9 also participating to a lesser extent [44]. *In vitro*, it behaves neither as a substrate nor as an inhibitor of P-gp [46,47]. Given its very broad pharmacokinetic variability, systematic monitoring of voriconazole plasma concentrations is recommended [48,49].

The available data indicate that the affinity of voriconazole for CYP3A4 is 50 times lower than for CYP2C9. [44] CYP2C19 activity is polymorphic [50–52].

Voriconazole is an inhibitor of the isoenzymes involved in its metabolism with IC_{50} values between approximately 8.5 (CYP2C) and 10.5 µM (CYP3A4) [53,35].

The prescribing information of this drug [43] points to the contraindication of voriconazole use with sirolimus or venetoclax given that voriconazole is likely to increase the plasma concentrations of both drugs and increase the risk of toxicity and, with the latter drug, tumor lysis syndrome [43].

Caution is advised when used in combination with glasdegib, since plasma concentrations of the latter drug may be elevated and there is a risk of QTc interval prolongation. If concomitant use cannot be avoided, frequent electrocardiogram monitoring is recommended.

Concomitant administration of voriconazole with tyrosine kinase inhibitors metabolized by CYP3A4 (such as bosutinib, dasatinib, nilotinib, ibrutinib, and ponatinib) is expected to increase plasma concentrations of the tyrosine kinase inhibitor and, with it, the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring are recommended [43].

There is also a risk of interactions with some commonly used immunosuppressants, such as cyclosporine (a dose reduction to half the dose of cyclosporine is recommended) and tacrolimus (a reduction to one third of the original dose is recommended) [43].

Voriconazole has been associated with QT interval prolongation and torsades de pointes ventricular tachycardia. [54–58] Concomitant administration of voriconazole with other drugs that can prolong QT and whose metabolism can be reduced by the antifungal drug is contraindicated due to the risk of QT prolongation and associated torsades de pointes [43]. It should also be used with caution in combination with any other drug that may prolong QT.

Posaconazole. Triazole with broad antifungal spectrum used particularly in the treatment of infections caused by *Aspergillus, Fusarium*, and *Mucor*. It can be administered intravenously and orally, as a solution or tablets, the latter having better bioavailability. It has an elimination half-life of 30 hours, high plasma-protein-binding (>95%) and a high volume of distribution [59–61].

The usual dose in the treatment of invasive fungal infection is to administer a loading dose of 300 mg (three 100 mg tablets or 300 mg of concentrate for solution for infusion) twice a day on the first day and then 300 mg (three 100 mg tablets or 300 mg of concentrate for solution for infusion) once a day [62]. Given the wide variability of pharmacokinetic parameters, especially when the solution formulation is used, it is necessary to recommend the systematic monitoring of plasma levels [63, 64].

Posaconazole is a potent inhibitor of CYP3A4, with IC_{50} values of 1.3 µM. In tablet formulation, it has more intense interactions related to increased bioavailability [65]. It is also a substrate of P-gp and exhibits inhibitory capacity for the transport protein, with an IC_{50} of 3 µM [47]; interactions with digoxin through this mechanism have been described [66]. Its metabolism is through glucuronide conjugation, with little involvement of the oxidative system [62,67].

Its prescribing information establishes the contraindi-

cation to its combination with sirolimus and the risks related to toxicity due to vincristine or vinblastine, venetoclax, cyclosporine tacrolimus, and all-transretinoic acid, all due to an increase in their plasma levels versus a reduction in their clearance [62].

As with the other azoles, posaconazole has been implicated in cases of QT prolongation and polymorphic ventricular tachycardia [68-71]. In relation to this, concomitant administration is contraindicated with CYP3A4 substrates that can also cause QT prolongation which may be related to the plasma concentrations reached. In addition, it should be used with caution in combination with any other drug that may prolong QT [62].

Isavuconazole. The newest azole antifungal, authorized for use in the treatment of invasive aspergillosis and mucor infection [72]. It may be administered orally or intravenously, the latter in the form of isavuconazonium sulfate, which undergoes hydrolysis by plasma esterases to form isavuconazole extremely quickly. It has excellent PO bioavailability, a large volume of distribution and high plasma-protein-binding [73,74]. Unlike other antifungals in its group, there is less variability in its pharmacokinetic parameters, so the systematic monitoring of its plasma levels is not recommended [75–78]. It is administered with a loading dose of 200 mg every 8 h for the first 48 h, which is followed by a maintenance dose of 200 mg every 24 h. Isavuconazole is both a substrate and inhibitor of isoenzyme CYP3A4 [79,80].

In vivo studies indicate that this antifungal is a moderate inhibitor of CYP3A4 and may weakly induce CYP2B6, mildly affecting other isoenzymes [81]. Probably in relation to this characteristic, it has been repeatedly described that the intensity of the interaction of isavuconazole with CYP3A4 substrates, such as immunosuppressants, is clearly lower than that produced by the other azoles [82]. Co-administration of isavuconazole with tacrolimus, sirolimus, or cyclosporine produced an increase in the AUC of the immunosuppressants of 125%, 84%, and 29%, respectively, and, in the case of mycophenolic acid and prednisolone, of 35 and 8%, respectively. The C_{max} values of tacrolimus, sirolimus, and cyclosporine increased by 42%, 65%, and 6%, respectively, while the C_{max} of mycophenolic acid and prednisolone were 11% and 4% lower, respectively [82].

Isavuconazole is described in its prescribing information as a moderate inhibitor of CYP3A4/5. Therefore, systemic exposure to drugs metabolized by CYP3A4 may increase if administered together with isavuconazole. As noted, concomitant use of isavuconazole with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus, or cyclosporine may increase systemic exposure to these drugs. Finally, careful monitoring of any incidence of toxicity is recommended, along with a reduction, if necessary, in the dose of vincristine, vinblastine, imatinib or mitoxantrone [72].

The administration of isavuconazole together with various substrates of transporter proteins was associated with insignificant changes in the pharmacokinetic parameters of atorvastatin, digoxin, metformin, and methotrexate [83]. The IC_{50} of isavuconazole on P-gp was 3 μM [47].

The effect of isavuconazole versus moxifloxacin or placebo on cardiac repolarization has been evaluated in a randomized double-blind study in healthy volunteers treated with the antifungal drug, including loading doses at conventional regimen and with supratherapeutic doses, for 11 days. No effect on QT interval prolongation has been demonstrated. In this study, a QT shortening effect related to the plasma concentrations of the drug was evidenced [84–86]. Isavuconazole is therefore contraindicated in patients with familial short QT syndrome; caution is advised when administering isavuconazole to patients who are taking other drugs known to decrease the QT interval, such as the antiepileptic drug rufinamide [72].

DRUGS USED IN HEMATOLOGY-ONCOLOGY

Table 2 describes the drugs commonly used in the treatment of hematological tumors and rejection prophylaxis in hematopoietic cell transplantation. This information has been used to select the drugs described in greater detail below because they may be targets for interaction with azoles due to alterations in their metabolism or at the level of the QT interval.

Acalabrutinib. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue of the active site of Bruton's tyrosine kinase. As a result, it is indicated for the treatment of chronic lymphocytic leukemia. It is eliminated from the body through the participation of the CYP3A4 isoenzyme, and is a substrate of the P-gp and BCRP transporter proteins. It has an elimination half-life of 1–2 h [87].

It has been reported that administration with itraconazole can increase the bioavailability of acalabrutinib by 4.8- to 5.2-fold [88]. Hence, it is recommended that concomitant use with CYP3A/gp-P inhibitors be avoided. If CYP3A/gp-P inhibitors (e.g. itraconazole, posaconazole, or voriconazole) are to be used for a short period, treatment should be discontinued [87].

The effect of moderate CYP3A inhibitors has been evaluated in healthy subjects by administering 400 mg of fluconazole in a single dose or 200 mg of isavuconazole in repeated doses for 5 days. The mean C_{max} and AUC values of acalabrutinib increased 1.37 (1.14–1.64) and 1.60 (1.45–1.77) times with isavuconazole and 1.48 (1.10–1.98) and 2.16 (1.94–2.40) times with fluconazole. For the active metabolite ACP-5862, these values were 0.72 (0.63–0.82) and 0.91 (0.86–0.97) times with isavuconazole and 0.65 (0.49–0.87) and 0.5 (0.91–0.99) times when co-administered with fluconazole [89]. No dose adjustment of acalabrutinib is required in combination with moderate CYP3A inhibitors [87].

QT prolongation has not been described in patients treated with this drug [87].

Bortezomib. This proteasome inhibitor is **indicated** for the treatment of mantle cell lymphoma and multiple myeloma. Bortezomib is metabolized mainly by oxidation through CYP3A4, CYP2C19, and CYP1A2, although the main metabolic pathway is deboronation, through which two deboronated

Table 2 **Drugs used in the treatment of hematologic tumors. Enzymes involved in its metabolism, involvement of transport proteins, and potential for QT prolongation**

	Enzymes	Transport proteins	QT prolongation
Acalabrutinib	3A4	P-gp, BCRP	
Bendamustine	1A2		
Bleomycin	Hydrolases		
Bortezomib	1A2, 3A4, 2C9		YES
Bosutinib	3A4		YES
Carfilzomib	Peptidases		YES
Cyclophosphamide	?		YES
Cyclosporine	3A4	P-gp, OATP	
Cisplatin	-		
Cytarabine	Cytidine deaminase		
Cladribine	Not known		
Chlorambucil	Various		
Dacarbazine	1A2, 2E1		
Dasatinib	3A4		YES
Doxorubicin	2D6, 3A4	P-gp	
Duvelisib	3A4		
Etoposide	3A4, UGT	P-gp	
Fludarabine	Phosphorylation		
Gemcitabine	Cytidine deaminase		
Gilteritinib	3A4	P-gp, BCRP	YES
Glasdegib	3A4, 2C8, UGT1A9		YES
Hydroxyurea	Various		
Ibrutinib	3A4		
Idelalisib	1A2, 3A4, UGT, AO	P-gp	
Imatinib	3A4		YES
Lenalidomide	-	P-gp	YES
Melphalan	Degradation		
6-mercaptopurine	Xanthine oxidase, various		
Methotrexate	Various		
Mycophenolate	UGT1A9		
Midostaurin	3A4		
Mitoxantrone	Various	BCRP	
Nilotinib	3A4	P-gp	YES
Oxaliplatin	-		YES
Pentostatin	-		
Pomalidomide	1A2, 3A4		
Ponatinib	3A4		YES
Prednisone	3A4		
Ruxolitinib	2C9, 3A4		
Selinexor	3A4, UGT		
Sirolimus	3A4	P-gp	
tacrolimus	3A4		YES
Thalidomide	-		
All-transretinoic acid	3A4		YES
Arsenic trioxide	-		YES
Venetoclax	3A4		
Vinblastine	3A4		
Vincristine	3A4	P-gp	

AO: aldehyde oxidase. P-gp: P-glycoprotein, BCRP: breast cancer resistance protein. OATP: organic anion transporting polypeptide.

metabolites are formed that subsequently undergo hydroxylation. It has an elimination half-life of 40–193 h in relation to self-inhibition of its metabolism [90].

In a drug-drug interaction study conducted in 12 patients to evaluate the effect of ketoconazole on the pharmacokinetics of bortezomib, a mean bortezomib AUC increase of 35% was observed. (CI 90% [1.032 to 1.772]) [91]. Although the percentage is of little clinical significance, cases of paralytic ileus have been described in patients treated with bortezomib, voriconazole or itraconazole [92]. Close monitoring is recommended when bortezomib is administered in combination with potent CYP3A4 inhibitors [90].

Isolated cases of QT interval prolongation were described in clinical trials; although causality has not been established [93], caution is recommended.

Bosutinib. It is a BCR-ABL tyrosine kinase inhibitor, indicated for the treatment of chronic myelogenous leukemia [94]. It is metabolized by CYP3A4, so inhibition of the activity of this isoenzyme leads to reduced clearance and increased concentrations. It has an elimination half-life of 35.5 h [94].

In a study of 24 healthy subjects who were administered 5 doses of 400 mg/day of ketoconazole together with a single 100 mg fasting dose of bosutinib, the C_{max} of bosutinib was increased by 5.2-fold, and the plasma AUC of bosutinib by 8.6-fold [95].

In a study of 20 healthy subjects administered a single 125 mg dose of aprepitant, a moderate CYP3A inhibitor, together with a single 500 mg dose of bosutinib after food, aprepitant increased bosutinib C_{max} by 1.5-fold and bosutinib AUC in plasma by 2.0-fold [96].

It is recommended to avoid concomitant use of bosutinib with potent or moderate CYP3A inhibitors, selecting, whenever possible, an alternative drug whose CYP3A inhibitory potential is null or minimal. If a potent or moderate CYP3A inhibitor is required during bosutinib treatment, it should be considered whether to discontinue or reduce the dose of bosutinib treatment. Caution should be exercised if weak CYP3A inhibitors are used with bosutinib [94].

In a randomized, single-dose, double-blind, crossover, open-label, placebo- and moxifloxacin-controlled study, the effect of bosutinib 500 mg administration on corrected QTc was evaluated in healthy subjects. According to the data from this study, bosutinib does not appear to prolong QTc in healthy subjects at a dose of 500 mg per day with food, nor under conditions that result in the supratherapeutic elevation of plasma concentrations. Following single-dose oral administration of bosutinib 500 mg (therapeutic dose) and bosutinib 500 mg together with 400 mg of ketoconazole (to achieve supratherapeutic concentrations of bosutinib) in healthy subjects, the upper limit of the one-sided 95% confidence interval (CI) around the mean change in QTc interval was less than 10 ms at all post-dose administration time points, and no adverse events suggestive of QTc prolongation were observed [97]. In a study in subjects with impaired liver function, an increasing frequency of QTc interval prolongation >450 ms was observed as liver function declined [98].

In the phase 1/2 clinical study conducted in patients with previously treated Ph+ leukemia, changes in the QTcF interval that differed >60 ms from the baseline interval were observed in 6 (1.1%) out of 562 patients. In the phase 3 clinical study in newly diagnosed chronic phase CML patients treated with bosutinib 400 mg, no patients in the bosutinib treatment group had an increase >60 ms relative to baseline when the QT interval was corrected with Fridericia's formula (QTcF). In the phase 3 clinical study in patients with newly diagnosed Ph+ CML in chronic phase treated with bosutinib 500 mg, changes in the QTcF interval that differed >60 ms from baseline were observed in 2 out of 248 (0.8%) patients receiving bosutinib [94]. The proarrhythmic potential of bosutinib cannot be ruled out [99].

In the light of these data, bosutinib should be used with caution in patients who have or may have QT interval prolongation, including patients with any overlapping risk factors. It is advisable to monitor for any effect on QTc, and a baseline electrocardiogram (ECG) is recommended before starting bosutinib treatment and when clinically indicated. Hypokalemia or hypomagnesemia should be corrected prior to bosutinib administration, and plasma concentrations of these ions should be monitored periodically during treatment [94].

Carfilzomib. Carfilzomib is a proteasome inhibitor that is metabolized primarily by the peptidase and epoxide hydrolase pathway and, consequently, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers [100]. QT interval prolongation and ventricular tachycardia have been reported [101].

Cyclophosphamide. It is a phosphoramide-type antineoplastic, of the nitrogen mustard group. It is an electrophilic agent, which acts specifically during the S phase of the cell cycle. It reacts with nucleophilic atoms of the nucleic bases, forming inter- and intra-chain bridges in the double helix DNA, causing important interferences in the processes of DNA transcription and replication. It is indicated for the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphomas, multiple myeloma, chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL), chronic myeloid leukemia, and acute lymphoblastic leukemia [102].

Increased exposure to cyclophosphamide metabolites has been reported in patients in treatment with itraconazole, fluconazole, and ketoconazole [102,103]. It has been suggested that, at least in the case of voriconazole, this effect could be caused by CYP2B6 inhibition [104]. In this regard, isavuconazole acts as an inducer of this isoenzyme, so it can *a priori* reduce cyclophosphamide concentrations with loss of efficacy [102], although some of the published data do not seem to confirm this [105].

Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including

atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmias) have been reported in patients with and without other signs of cardiotoxicity [106].

Cyclosporine. Cyclosporine is a calcineurin inhibitor immunosuppressant indicated for the prevention of graft rejection after allogeneic bone marrow and stem-cell transplantation and in the prevention or treatment of graft-versus-host disease (GVHD). It is extensively metabolized, resulting in the formation of 15 metabolites. Metabolism takes place mainly in the liver, via CYP3A4 [107].

Caution should be exercised when cyclosporine is co-administered with drugs that produce CYP3A4 and/or P-glycoprotein inhibition. The azole antifungals: fluconazole, itraconazole and voriconazole can at least double exposure to cyclosporine [108–113].

In a retrospective study, information was collected from bone marrow transplant patients treated with tacrolimus or cyclosporine and fluconazole, isavuconazole, or posaconazole. The dose reduction percentage needed to maintain levels within the therapeutic range for the three azoles was 27, 12, and 13%, respectively [113].

In a study conducted in children with bone marrow transplant treated with cyclosporine or tacrolimus or sirolimus in which a dose of 100/200 mg of isavuconazole was used, no interactions were described [114].

A study was conducted to evaluate the effect of posaconazole 200 mg daily for 10 days on cyclosporine. Coadministration of posaconazole increased the bioavailability of cyclosporine and the dose should be reduced by 14–29% [115].

Dasatinib. Dasatinib is an inhibitor of several tyrosine kinases; BCR-ABL, SRC, c-KIT and PDGFR, which is indicated for the treatment of newly diagnosed chronic myelogenous leukemia (CML) in the chronic, accelerated or blastic phase, Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) and lymphoid blast crisis from CML. It is a substrate of the CYP3A4 isoenzyme, so potent inhibitors of this enzyme may increase its bioavailability. As a result, coadministration of potent CYP3A4 inhibitors in patients receiving dasatinib is not recommended. It has an elimination half-life of 3–5 h [116].

In a study in which dasatinib was administered with ketoconazole for 8 days, the C_{max} increased from 14 ng/mL on day 2 to 51 ng/mL on day 8. The AUC was 71 ng*h/mL and 345 ng*hour/mL, respectively. The C_{max} and AUC ratios, from day 8 to day 2, were 3.56 (90% CI, 2.86–4.44) and 4.84 (90% CI, 3.83–6.13), respectively. In addition, the elimination half-life increased from 3.3 hours to 8.7 hours [117]. Therefore, coadministration of potent CYP3A4 inhibitors is not recommended [116].

In vitro and in vivo data suggest that dasatinib has the ability to prolong ventricular cardiac repolarization (QT interval) [118,119]. In 258 patients treated with dasatinib and 258 patients treated with imatinib, after a minimum follow-up of 60 months in the phase 3 trial in patients with CML, QTc prolongation was reported as an adverse reaction in 1 patient (<1%) in each group. The median change in QTcF from baseline was 3.0 ms in dasatinib-treated patients compared with 8.2 ms in imatinib-treated patients. One patient (<1%) in each group experienced a QTcF >500 ms. In 865 patients with leukemia treated with dasatinib in phase 2 clinical studies, the mean change in QTc interval from baseline values using the Fridericia (QTcF) method was 4–6 ms, with an upper limit at the 95% confidence interval < 7 ms. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical trials, 15 (1%) patients had QTc prolongation as an adverse reaction and 21 patients (1%) had a QTcF >500 ms [116].

Dasatinib should be administered with caution in patients who have or may develop QTc prolongation. This includes patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic drugs or other drugs that cause QT prolongation, and patients in treatment with high cumulative doses of anthracyclines. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration [116].

Doxorubicin. Doxorubicin is an anthracycline antibiotic, substrate of CYP3A4, CYP2D6 and P-glycoprotein. Clinically significant interactions with CYP3A4, CYP2D6 and/or P-glycoprotein inhibitors have been reported, resulting in increased concentrations and clinical effect of doxorubicin [120]. However, doxorubicin and ketoconazole have been evaluated in combination in the treatment of prostate cancer without reporting effects related to a possible interaction [121]. Doxorubicin has not been implicated in alterations of cardiac repolarization.

Duvelisib. Duvelisib is an inhibitor of phosphatidylinositol 3-kinase p110δ (PI3K-δ) and PI3K-γ indicated for the treatment of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). It is eliminated from the body after metabolism by CYP3A4 [122].

Concomitant administration of a strong CYP3A inhibitor, ketoconazole (200 mg twice daily for 5 days), with a single oral dose of 10 mg duvelisib in healthy adults (n = 16) increased 1.7-fold the C_{max} of duvelisib and 4-fold the AUC. It is recommended to reduce the dose to 15 mg twice daily when administered concomitantly with potent CYP3A4 inhibitors. No dose adjustment is necessary when administered with moderate CYP3A4 inhibitors, although potential adverse reactions to duvelisib should be closely monitored [122].

The effect of different doses of duvelisib 25 and 75 mg twice daily on the corrected QT interval (QTc) was evaluated in patients with previously treated hematologic malignancies. No increases >20 ms were observed in the QTc interval [122].

Etoposide. This is a cytostatic whose main effect appears to focus on double-strand DNA breaks through interaction

with topoisomerase II or through the formation of free radicals. It is indicated for the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma, and acute myeloid leukemia [123].

It is a substrate of CYP3A4 and P-gp and undergoes glucuronide conjugation. Ketoconazole increases the AUC of etoposide by 20% so no dose adjustment is required; however, toxicity should be monitored [124].

Gilteritinib. Inhibitor of FMS-like tyrosine kinase-3 (FLT3) or fetal liver kinase 2, and AXL that is indicated for the treatment of acute myeloid leukemia with FLT3 mutation [125]. According to *in vitro* data, gilteritinib is metabolized primarily through CYP3A4. In addition, it is a substrate of P-gp and BCRP. Gilteritinib could inhibit BCRP, P-gp and OCT1 at clinically relevant concentrations [125].

In healthy subjects, a single 10 mg dose of gilteritinib administered with itraconazole (200 mg once daily for 28 days), resulted in an approximate 20% increase in mean C_{max} and a 2.2-fold increase in mean AUC compared to subjects given a single dose of gilteritinib [125]. Exposure to gilteritinib increased approximately 1.5-fold in patients with relapsed or refractory AML when it was co-administered with a potent inhibitor of CYP3A, P-gp and/or BCRP [126].

Potent inhibitors of CYP3A, P-gp and/or BCRP (voriconazole, itraconazole, posaconazole) may increase plasma concentrations of gilteritinib. Alternative drugs that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where there are no suitable therapeutic alternatives, toxicity should be carefully monitored during the administration of gilteritinib [125].

Gilteritinib may prolong cardiac ventricular repolarization. QT interval prolongation can be observed in the first three months of treatment with this drug [127]. It is recommended to discontinue administration of the drug if the QTcF interval is greater than 500 ms and to resume treatment reducing the dose to 80 mg or 120 mg when the QTcF interval returns to within 30 ms of the baseline level or ≤480 ms. If an increase in the QTcF interval >30 ms occurs on ECG on day 8 of cycle 1, it should be confirmed by ECG on day 9, after which a dose reduction to 80 mg should be considered [125].

Glasdegib. It is an inhibitor of the Hedgehog signal transduction pathway that is indicated for the treatment of *de novo* or newly diagnosed secondary acute myeloid leukemia (AML) in adult patients who are not candidates for standard induction chemotherapy, in combination with low-dose cytarabine. CYP3A4 is responsible for most of the metabolism of glasdegib while CYP2C8 and UGT1A9 play a minor role [128].

Ketoconazole, at a dose of 400 mg once daily for 7 days, increased the mean area under the curve of glasdegib approximately 2.4-fold and the maximum plasma concentration by 40%, after administration of a single oral dose of 200 mg, in healthy subjects [129].

Caution should be exercised when it is administered concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, posaconazole and voriconazole, since an increase in the plasma concentration of glasdegib may occur. If possible, an alternative concomitant drug with no or minimal CYP3A4 inhibitory potential is recommended [128].

In a randomized study in patients with high-risk acute myeloid leukemia and myelodysplastic syndrome treated with glasdegib and low-dose cytarabine versus low-dose cytarabine monotherapy, Grade 3/4 QT prolongations on ECGs were reported in 3.5% of patients treated with glasdegib and low-dose cytarabine compared to 2.4% of patients treated with low-dose cytarabine monotherapy [130].

Alternatives should be considered for drugs with known effects on QT prolongation and/or those that are potential potent CYP3A4 inhibitors [128].

Ibrutinib. This is a Bruton's tyrosine kinase (BTK) inhibitor used in the treatment of relapsed or refractory mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Waldenström macroglobulinemia [131]. Ibrutinib is metabolized primarily by CYP3A4, generating a dihydrodiol metabolite with approximately 15-fold lower BTK inhibitory activity than ibrutinib. The involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal. It has an elimination half-life of 4–13 h [131].

Combination with CYP3A4 inhibitors alters the clearance of ibrutinib. Co-administration with itraconazole produces a 10-fold increase in the AUC of ibrutinib and an 8.8-fold increase in the C_{max} [132]. Concomitant administration of ketoconazole to 18 healthy, fasting volunteers increased the C_{max} and AUC of ibrutinib 29-fold and 24-fold, respectively. In patients with B-cell malignancies treated with ibrutinib, concomitant administration of voriconazole increased C_{max} 6.7-fold and AUC 5.7-fold [133,134].

Potent CYP3A4 inhibitors (itraconazole, voriconazole, and posaconazole) should be avoided. If the benefit outweighs the risk and a potent CYP3A4 inhibitor must be used, the dose of ibrutinib should be reduced to 140 mg during treatment with the inhibitor or ibrutinib should be temporarily discontinued, for 7 days or less. The patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed [131].

Moderate CYP3A4 inhibitors produce a lower intensity effect, as has been shown with erythromycin, in patients with B-cell neoplasms in which the C_{max} and AUC of ibrutinib increased 3.4-fold and 3.0-fold, respectively. It is recommended to reduce the dose to 280 mg for as long as the inhibitor is used. The patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed. Fluconazole – and probably isavuconazole – are part of this recommendation. As can be deduced from the results of a retrospective study in which information was collected from eight patients treated with the combination of isavuconazole (200 mg/day) and ibrutinib for fungal infection, the effect of this azole is minor. Five patients remained on the initial dose of ibrutinib (140–420 mg/day), while, in the remaining three,

the dose was reduced from 420/mg/day to 140–280 mg/day. In seven of the patients, the evolution of the fungal infection was adequate, with no adverse effects. In one patient, ibrutinib had to be discontinued due to thrombopenia after 128 days of combined treatment with isavuconazole [135].

No dose adjustment of ibrutinib appears necessary when combined with mild CYP 3A4 inhibitors, since it is estimated that the AUC may increase less than 2-fold. However, the patient should be closely monitored for toxicity, and dosage modification guidelines should be followed as needed [131].

The effect of ibrutinib on the QTc interval was evaluated in 20 healthy men and women in a randomized, double-blind, placebo-controlled, positive-controlled study. At the supratherapeutic dose of 1,680 mg, ibrutinib did not prolong the QTc interval in a clinically significant manner. The largest upper limit of the bilateral 90% CI for differences in the baseline-adjusted mean between ibrutinib and placebo was less than 10 ms. In the same study, a concentration-dependent reduction in the QTc interval (-5.3 ms [90% CI: -9.4, -1.1] was observed at a C_{max} of 719 ng/mL followed by a supratherapeutic dose of 1,680 mg [136].

Idelalisib. Idelalisib is an inhibitor of phosphatidylinositol 3-kinase p110ć (PI3K-p110) and Bruton's tyrosine kinase (BTK) protein, indicated for the treatment of chronic lymphocytic leukemia and follicular lymphoma. Idelalisib is metabolized mainly by an aldehyde oxidase and, to a lesser extent, by CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP. The elimination half-life is 8.2 hours (range: 1.9–37.2) [137].

In a clinical trial, concomitant administration of a single 400 mg dose of idelalisib with 400 mg once daily of ketoconazole was found to generate a 26% increase in the C_{max} and 79% increase in the AUC of idelalisib. [138] No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but intensified monitoring for adverse reactions is recommended [137].

The effect of idelalisib (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled crossover trial (moxifloxacin 400 mg) in 40 healthy subjects. At a dose 2.7 times the maximum recommended dose, idelalisib did not prolong the QT/QTc interval (<10 ms) [137].

Imatinib. Imatinib is a BCR-ABL tyrosine kinase inhibitor that can be used in the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (BCR-ABL), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), myelodysplastic/myeloproliferative syndromes, advanced hypereosinophilic syndrome and/or chronic eosinophilic leukemia. It has an elimination half-life of 18 h [139].

In vitro results show that CYP3A4 is the major human P450 enzyme catalyzing the biotransformation of imatinib. Inhibitors of CYP3A4 activity; azole antifungals including ketoconazole, itraconazole, posaconazole and voriconazole, could reduce metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib. The mean C_{max} and AUC of imatinib increased by 26% and 40%, respectively, in healthy subjects when co-administered with a single dose of ketoconazole [139].

Experimental models have shown a clear effect of voriconazole on the clearance of imatinib, which is significantly reduced, with an increase in C_{max} of 36.8% [140]. Serious adverse effects in the form of a pustular rash, probably concentration dependent, have been described in a patient treated with voriconazole and imatinib [141]. Caution should be exercised when imatinib is administered with inhibitors of the CYP3A4 family.

Imatinib can cause QT prolongation in some patients, probably with a lower incidence than the other drugs used for the treatment of chronic myeloid leukemia [118,142].

Lenalidomide. Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1 (DDB1), cullin 4 (CUL4) and regulator of cullins 1 proteins (Roc1). In hematopoietic cells, lenalidomide bound to cereblon recruits the substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation, which produces direct cytotoxic and immunomodulatory effects. It is indicated for the treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma [143].

In vitro, lenalidomide is a substrate of P-gp, but does not exhibit inhibitory capacity. P-gp inhibitors do not appear to have any relevant effects on lenalidomide pharmacokinetics [144].

Occasionally, arrhythmia, QT interval prolongation, atrial flutter and ventricular extrasystoles have been described among the infrequent adverse effects of the drug [143,145]. Lenalidomide did not produce QT alterations in a study performed with therapeutic and supratherapeutic doses [146].

Midostaurin. Midostaurin is an inhibitor of FLT3, KIT, PDGFR (platelet growth factor receptor) and VEGFR2 (vascular endothelial growth factor receptor 2), and serine/threonine kinase of the protein kinase C (PKC) family. It is indicated in the treatment of acute myeloid leukemia (AML) with FLT3 mutation in combination with standard induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL). Its elimination half-life is 20.9 h [147].

Midostaurin undergoes extensive hepatic metabolism, mainly through CYP3A4, and transformed into the active metabolites CGP62221 and CGP52421. In a clinical trial of 36 healthy subjects, steady-state administration of ketoconazole with a single 50 mg dose of midostaurin resulted in a significant increase in midostaurin concentrations, C_{max} and AUC

were 1.8-fold and 10-fold higher, respectively. In addition, there was a 3.5-fold increase in the AUC of CGP62221 [148].

In a group of patients treated with itraconazole, a potent CYP3A4 inhibitor, at steady state, and with midostaurin at steady state (50 mg twice daily for 21 days), the steady state concentration of midostaurin, (C_{min}) increased 2.09-fold. The C_{min} of CGP52421 increased by a factor of 1.3, while no significant effect on CGP62221 exposure was observed [147].

Recently, an 8-fold increase in midostaurin concentration has been described when administered in association with posaconazole [149]. The use of isavuconazole and midostaurin is anecdotal, but the presence of interactions has not been described [150, 151].

Caution is recommended when potent CYP3A4 inhibitors are administered concomitantly with midostaurin because they may increase plasma concentrations of midostaurin. Alternative drugs that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity [147].

A specific study on the QT interval in 192 healthy subjects who received the 75 mg dose twice daily did not show that midostaurin or CGP62221 prolonged the QT interval in a clinically significant manner. However, this study was of insufficient duration to estimate the effects of the long-acting metabolite CGP52421 on QTc interval prolongation [152]. Consequently, a phase 2 clinical trial on 116 patients with ASM, SM-AHN, or MCL studied the change to QT corrected with Fridericia's formula (QTcF) with respect to baseline with the concentration of midostaurin and each metabolite, and the result showed that neither midostaurin, nor CGP62221 or CGP52421 appeared to be able to cause a clinically significant prolongation of QTcF. In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one QTcF measurement greater than 450 ms and 4.7% greater than 480 ms on ECG [147].

Therefore, caution should be exercised in patients at risk of QTc prolongation (e.g. due to concomitant medications and/or electrolyte disturbances). If midostaurin is taken with other drugs that prolong the QT interval, consideration should be given to assessing the QT interval by ECG. If QT prolongation is detected, the dose should be adjusted [147].

- QTc interval >470 ms and ≤500 ms

Decrease the dose to 50 mg once daily for the remaining cycle. Restart at the initial dose in the next cycle if the QTc interval improves to ≤470 ms at the start of the cycle. Otherwise, continue with midostaurin 50 mg once daily.

- QTc interval >500 ms

Stop or discontinue in the remaining cycle. If, just before the next cycle, the QTc interval improves to ≤470 ms, restart at the initial dose. If the QTc interval does not improve at the beginning of the next cycle, do not administer during that cycle. Midostaurin can be stopped for as many cycles as necessary until the QTc interval improves.

Nilotinib. Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein. It also inhibits PDGF, KIT and Ephin receptor kinases. It is indicated for the treatment of Philadelphia chromosome positive chronic myeloid leukemia. Nilotinib is metabolized primarily in the liver by CYP3A4, the expected major oxidative metabolizer, and nilotinib is also a substrate of P-gp [153]. Its elimination half-life is 17 h.

Exposure to nilotinib in healthy subjects increased 3-fold when co-administered with ketoconazole [154]. Therefore, concomitant treatment with potent CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, should be avoided. Increased exposure to nilotinib may also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medications with no or minimal inhibition of CYP3A4 should be considered [153].

In the phase III trial in newly diagnosed chronic phase CML patients receiving 300 mg of nilotinib twice daily, the change in mean QTcF interval time from baseline at steady state was 6 ms. No patient presented a QTcF >480 ms. No episodes of torsades de pointes were observed. In a trial with healthy volunteers with exposures comparable to those observed in patients, no clinically relevant arrhythmias were observed [153]. However, nilotinib has been shown to prolong ventricular cardiac repolarization in a concentration-dependent manner in both adult patients and children [155,156].

Nilotinib may produce significant QT interval prolongation when administered with potent CYP3A4 inhibitors, with drugs with a known ability to prolong the QT interval and/or with food. The presence of hypokalemia and hypomagnesemia may increase this effect. Nilotinib should be used with caution in patients who have or are at significant risk of developing QTc interval prolongation [153].

Oxaliplatin. Oxaliplatin interacts with DNA forming inter- and intra-strand cross-links causing disruption of DNA synthesis resulting in cytotoxic and anti-tumor effects [157].

QT prolongation and torsades de pointes have been described in patients treated with oxaliplatin [158,159]. The QT interval should be closely and regularly monitored before and after oxaliplatin administration. Caution should be exercised in patients with a history of or a predisposition for QT prolongation, those taking medications known to prolong the QT interval, and those with electrolyte imbalances such as hypokalemia, hypocalcemia, or hypomagnesemia. In case of QT prolongation, treatment with oxaliplatin should be discontinued [157].

Pomalidomide. Indicated for the treatment of multiple myeloma, it is partly metabolized by CYP1A2 and CYP3A4/5. It is also a substrate for P-gp [160]. Concomitant administration of pomalidomide with ketoconazole, a potent inhibitor of CYP3A4/5 and P-gp, demonstrated no clinically relevant effect on pomalidomide exposure [160,161]. In a study in healthy volunteers that compared the effect on QT of pomalidomide 4 mg, 20 mg, and moxifloxacin 400 mg, pomalidomide did not

generate ECG alterations, versus the evident QT prolongation produced by fluoroquinolone [162].

Ponatinib. Ponatinib inhibits the activity of BCR-ABL and RET, FLT3 and KIT and members of the FGFR, PDGFR and VEGFR kinase families. It is indicated for the treatment of chronic phase chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). It has an elimination half-life of 22 hours [163]. Ponatinib is metabolized by the action of CYP3A4. Concomitant administration of a single 15 mg oral dose of ponatinib and ketoconazole 400 mg daily moderately increased systemic exposure to ponatinib; the AUC and C_{max} values of ponatinib were 78% and 47% higher, respectively, than those observed when ponatinib was administered as monotherapy [164]. Caution is required and a reduction of the initial dose of ponatinib to 30 mg should be considered when it is used concomitantly with strong CYP3A inhibitors.

The potential of ponatinib to prolong the QT interval was evaluated in 39 leukemia patients; no clinically significant prolongation of the QT interval was observed [165]. However, a thorough study of the QT interval has not been performed, so a clinically important effect on QT cannot be ruled out, and it is considered a risk drug.

Prednisone. Most corticosteroids undergo metabolism through CYP3A4. Concomitant treatment with CYP3A inhibitors such as ketoconazole and itraconazole has been shown to reduce corticosteroid clearance, increasing the risk of systemic adverse reactions [167]. This combination should be avoided unless the benefit outweighs the risk, in which case patients should be monitored for systemic reactions to corticosteroids [167].

No association has been described between the use of corticosteroids and the presence of QT prolongation or with torsades de pointes.

Ruxolitinib. Ruxolitinib is a selective inhibitor of the Janus-associated kinases (JAKs): JAK1 and JAK2. It is indicated for the treatment of myelofibrosis and polycythemia vera. It has an elimination half-life of 3 hours. Ruxolitinib is eliminated through metabolism by CYP3A4 and CYP2C9. Therefore, drugs that inhibit these enzymes may cause increased exposure to ruxolitinib [168].

In healthy subjects the co-administration of ruxolitinib, 10 mg single dose, with a potent CYP3A4 inhibitor, ketoconazole, increased the C_{max} and AUC of ruxolitinib by 33% and 91%, respectively. With concomitant administration of ketoconazole, the half-life was prolonged from 3.7 to 6.0 hours [169].

When administering ruxolitinib together with potent CYP3A4 inhibitors, including itraconazole, voriconazole and posaconazole, the dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dosage should be titrated based on safety and efficacy [168]. If ruxolitinib is administered together with potent CYP3A4 inhibitors or dual inhibitors of the CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the dose of Jakavi should be reduced by approximately 50%, and administered twice daily [168].

In healthy subjects, co-administration of ruxolitinib, 10 mg single dose, with erythromycin, a moderate CYP3A4 inhibitor, 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC values that were higher by 8% and 27%, respectively [169]. No dose adjustment is required when ruxolitinib is administered with mild or moderate CYP3A4 inhibitors. However, patients should be closely monitored.

In healthy subjects, concomitant administration of ruxolitinib, 10 mg as a single dose, and a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, elevated the C_{max} and AUC of ruxolitinib by 47% and 234%, respectively [170]. When using drugs that are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), a 50% dose reduction should be considered. The concomitant use of ruxolitinib with daily doses of fluconazole greater than 200 mg should be avoided. It has been reported that the co-administration of 400 mg daily of voriconazole with ruxolitinib was effective and well tolerated, despite being a dual inhibitor of CYP3A4 and CYP2C9 [171].

In a detailed study of the QT interval in healthy subjects, no indication of a QT/QTc prolonging effect was observed when ruxolitinib was administered at single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarization [172].

Selinexor. Selinexor is a covalent and reversible selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1). XPO1 is the primary mediator of nuclear export of a large number of cargo proteins, including tumor suppressor proteins (TSPs), growth regulators and growth-promoting (oncogenic) protein mRNAs. It is indicated for the treatment of multiple myeloma. Selinexor is metabolized by CYP3A4, various UDP-glucuronosyltransferases (UGTs) and glutathione-S-transferases (GSTs) [173].

No specific clinical studies on drug-drug interactions have been performed. A 30–40% increase in the AUC of selinexor when the drug was administered with azole antifungals has been described in a study in rats [174]. Dosage adjustments may not be necessary when the drug is used in combination with potent CYP3A4 inhibitors, although caution should be exercised.

The effect of various doses of selinexor up to 175 mg twice weekly on the QTc interval was evaluated in patients with hematologic malignancies in whom several treatments had been administered previously. Selinexor did not have a large effect (i.e. no greater than 20 ms) on the QTc interval when administered at the therapeutic dose level [173].

Sirolimus. Sirolimus binds to the specific cytosolic protein FKPB-12 forming an FKPB 12-sirolimus complex that inhibits the activation of the mammalian target of rapamycin molecule (mTOR), a critical kinase for cell cycle progression [175].

Sirolimus is extensively metabolized in the intestinal wall and liver by the CYP3A4 isoenzyme. Sirolimus is also a substrate for P-gp located in the small intestine. Administration of repeated doses of ketoconazole significantly altered sirolimus exposure when administered as an oral solution, with increases in sirolimus C_{max}, t_{max} and AUC values by 4.4-fold, 1.4-fold and 10.9-fold, respectively. [176] Co-administration of sirolimus and ketoconazole is not recommended [175].

Co-administration of sirolimus, a single dose of 2 mg, with multiple doses of oral voriconazole, 400 mg every 12 hours on day 1, then 100 mg every 12 hours for 8 days, in healthy subjects has been reported to increase the C_{max} and AUC of sirolimus by 7- and 11-fold, respectively. Co-administration of sirolimus and voriconazole is not recommended, although it has been suggested that, if used together, the dose of the immunosuppressant should be reduced by 50% [177] and 90% [178].

With posaconazole, the dose should be reduced by 60–80% [179,180], although some agencies have considered it necessary to contraindicate the combined use of sirolimus and posaconazole, describing that the administration of 200 mg of the antifungal drug in tablet form can increase the C_{max} and AUC of the immunosuppressant by 527% and 788%, respectively [62].

Isavuconazole also increases the AUC of sirolimus, but by much less: about 1.5 times, so the need for initial dose adjustment is less important [181].

Tacrolimus. Tacrolimus binds to a cytosolic protein forming a complex, FKBP12-Tacrolimus, which specifically and competitively binds to and inhibits calcineurin. This results in a calcium-dependent inhibition of T-cell signal transduction pathways, which prevents transcription of a discrete set of lymphokine genes. Tacrolimus is metabolized by CYP3A4 and undergoes the intestinal first-pass effect through the intervention of this isoenzyme [182].

Voriconazole significantly increases the tacrolimus concentration/dose ratio from 172.8 to 537.5 [183]. The increased bioavailability of tacrolimus is higher when voriconazole is switched from the intravenous to the oral route, as a result of the alteration of intestinal CYP3A4 that occurs with the oral route and is absent with intravenous administration [184]. It has been suggested that the dose of tacrolimus be reduced by at least 50% when initiating treatment with voriconazole [185].

With posaconazole, the AUC of tacrolimus increases 3-fold in lung transplant patients treated with antifungal tablets [186]; a 50% [187] or 60–70% reduction in the dose of the immunosuppressant is recommended [188]. The administration of posaconazole at a dose of 400 mg together with tacrolimus increased the C_{max} and AUC of tacrolimus by 121% and 358%, respectively [115].

With isavuconazole, it does not appear necessary to adjust the tacrolimus dose at the start of treatment [189], although it has been recommended that an initial tacrolimus dose of 0.017 mg/kg be administered instead of the usual 0.02 mg/kg [190]. In the case of liver transplantation, a 30% dose reduction was recommended [191]. The combination of isavuconazole and tacrolimus increased the concentration/dose ratio of the immunosuppressant 1.42-fold in the first week of treatment [181].

In a retrospective study with information collected from bone marrow transplant patients treated with tacrolimus and fluconazole, isavuconazole, or posaconazole, the percentage dose reduction needed to maintain levels within the therapeutic range for the three azoles was 25, 21 and 53%, respectively [192].

Occasional cases of QT prolongation associated with tacrolimus have been reported [193], so close monitoring of blood levels and assessment of the QT interval, renal function, and other adverse effects of tacrolimus is recommended when drugs with the potential to alter CYP3A4 metabolism are used concomitantly, and the tacrolimus dose should be discontinued or adjusted appropriately to maintain similar tacrolimus exposure [193,194].

All-transretinoic acid. It is indicated for the treatment of acute promyelocytic leukemia [195]. Tretinoin is metabolized by CYP26A1 in addition to CYP3A4. Compounds that inhibit CYP26A1, such as ketoconazole, could result in increased exposure to tretinoin. There is still no clinical evidence on the relative involvement of this enzyme in the general metabolism of tretinoin [195].

Increased tretinoin toxicity has been reported (e.g. pseudotumor cerebri, hypercalcemia) when azole antifungals were administered (e.g. fluconazole, voriconazole, posaconazole). This appears to be the result of a pharmacokinetic interaction involving mainly CYP3A4 [196,197]. The possibility of reducing the tretinoin dose should be considered [195].

QTc prolongations were observed with tretinoin and arsenic trioxide combination therapy. This could lead to torsades de pointes arrhythmias. For the treatment of QTc prolongation, ECG monitoring prior to and during treatment is recommended, especially for patients with risk factors [198].

Arsenic trioxide. The metabolism of arsenic trioxide involves the oxidation of arsenious acid, the active species of arsenic trioxide, to arsenic acid, as well as oxidative methylation to monomethylarsonic and dimethylarsinic acid mediated by methyltransferases, which takes place mainly in the liver. It is indicated for the treatment of acute promyelocytic leukemia [199].

Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. Prolongation of the QT interval can produce ventricular arrhythmia in torsades de pointes, which can lead to death. Prior treatment with anthracyclines may increase the risk of QT interval prolongation. The risk of ventricular tachycardia in torsades de pointes is higher in patients who are receiving or have received drugs that cause hypokalemia or hypomagnesemia, such as diuretics or am-

Table 3 Azoles in hematology-oncology. Recommendations

	Itraconazole	Posaconazole	Voriconazole	Isavuconazole
Acalabrutinib	Avoid or reduce the dose of acalabrutinib to 100 mg/day			No dose titration. Monitor adverse effects
Bortezomib	Caution (1)			Probably without risk
Bosutinib	Avoid. Risk of QT prolongation due to elevated bosutinib concentrations			Caution. (2) Reduce the dose by 50%
Carfilzomib	Caution. Risk of QT prolongation			Without risk
Cyclophosphamide	Caution: May increase cyclophosphamide levels with potential risk of QT prolongation			Risk of potential ineffectiveness (3)
Cyclosporine	Caution. Elevated cyclosporine levels	Reduce cyclosporine dose by 75%	Reduce cyclosporine dose by 50 %	Caution (4)
Dasatinib	Avoid. Risk of QT prolongation due to elevated dasatinib concentrations			No dose titration. Monitor adverse effects
Doxorubicin	No dose titration. Monitor adverse effects			
Duvelisib	Reduce duvelisib dose to 15 mg twice daily			No dose titration. Monitor adverse effects
Etoposide	No dose titration. Monitor adverse effects			
Gilteritinib	Avoid or closely monitor			No dose titration. Monitor adverse effects
Glasdegib	Avoid. Risk of QT prolongation due to elevated glasdegib concentrations			Without risk
Ibrutinib	Avoid	Caution (5)		Caution (6)
Idelalisib	Without risk			
Imatinib	Caution (7)			
Lenalidomide	No dose titration. Monitor adverse effects (8)			No dose titration
Midostaurin	Caution. Alternative drugs that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.			Monitor adverse effects
Nilotinib	The administration of nilotinib with drugs that are strong CYP3A4 inhibitors should be avoided (9)			No dose titration. Monitor adverse effects
Oxaliplatin	No dose titration. Monitor adverse effects (8)			No dose titration
Pomalidomide	No dose titration. Monitor adverse effects			
Ponatinib	Caution, consider reducing the starting dose of ponatinib to 30 mg			No dose titration. Monitor adverse effects
Prednisone	Caution (10)			Caution (11)
Ruxolitinib	Caution	Reduce ruxolitinib dose by 50%		No dose titration. Monitor adverse effects
Selinexor	No dose titration. Monitor adverse effects			
Sirolimus	Avoid			Caution (4)
tacrolimus	Caution (12)	Reduce tacrolimus dose by one third		Caution (4)
All-transretinoic acid	Caution (13)			No dose titration. Monitor adverse effects
Arsenic trioxide	Caution (8)			Without risk
Venetoclax	Avoid (14)			Reduce the daily dose by 50%
Vinblastine	Avoid	Caution (15)	Caution (16)	Caution (16)
Vincristine	Avoid	Caution (15)	Caution (16)	Caution (16)

(1): Paralytic ileus cases have been described in patients treated with bortezomib, voriconazole or itraconazole.
(2) It can likely be used with caution since the contraindication is due to the risk of QT prolongation relating to increased concentrations due to CYP3A5 inhibition, which are lower with this drug.
(3): Isavuconazole is a mild inducer of CYP2B6.
(4) If necessary, monitor plasma levels to adjust the dose of the immunosuppressant.
(5): Reduce the dose to 140 mg/day in B-cell tumors and to 280 mg/day in the case of graft-versus-host disease.
(6) Reduce the dose to 280 mg/day in B-cell tumors and to 420 mg/day in graft-versus-host disease.
(7) Careful monitoring of any incidence relating to drug toxicity. Reduce the dose if necessary.
(8) Potential risk; both drugs can prolong QT.
(9) Significant QT interval prolongation can occur when nilotinib is administered inappropriately with potent CYP3A4 inhibitors.
(10) Risk of increased corticosteroid concentrations. Monitor adverse effects.
(11) Co-administration should be avoided unless the potential benefit outweighs the risk of increased concentrations.
(12) Use only if there are no other alternatives.
(13): Increased tretinoin concentrations with risk of toxicity. Monitor plasma calcium levels and assess dose reduction.
(14) Avoid at initiation and during the dose-titration phase; risk of tumor lysis syndrome. Reduce the daily dose of venetoclax by 75% when administered as a fixed daily dose.
(15) Only use when there are no alternative antifungal treatment options.
(16) Risk of neurotoxicity due to high concentrations of alkaloids. It may be necessary to reduce the dose.

photericin B. Caution is advised when arsenic trioxide is administered concomitantly with other drugs that prolong the QT/QTc interval, or drugs that cause hypokalemia or hypomagnesemia [200–202].

Venetoclax. Venetoclax is a potent and selective inhibitor of the anti-apoptotic protein BCL-2 (B-cell lymphoma). It is used in the treatment of chronic lymphocytic leukemia and acute myeloid leukemia. It has an elimination half-life of 26 hours. Venetoclax is metabolized mainly by CYP3A [203].

In a study in 11 patients, concomitant administration of ketoconazole 400 mg once daily for 7 days increased venetoclax C_{max} 2.3-fold and AUC 6.4-fold [204]. Compared with monotherapy administration of 400 mg venetoclax, concomitant administration of posaconazole 300 mg, venetoclax 50 mg and 100 mg for 7 days in 12 patients increased the C_{max} and AUC of venetoclax 1.6- and 1.9-fold, and 1.9-, and 2.4-fold, respectively [205].

Concomitant administration of venetoclax with other potent CYP3A4 inhibitors is expected to increase the AUC by an average of 5.8- to 7.8-fold [203].

In an uncontrolled study, the administration of conventional doses of isavuconazole as antifungal prophylaxis in 65 patients with acute myeloid leukemia or myelodysplastic syndrome, 49% of whom were treated with venetoclax, was effective and well tolerated, with no significant adverse effects reported [206].

Concomitant use of venetoclax with moderate or strong CYP3A inhibitors increases the C_{max} and AUC of venetoclax and may increase the risk of tumor lysis syndrome (TLS) and other toxic effects, at initiation and during the dose-titration phase. In patients with CLL, concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated. If the use of a CYP3A inhibitor is essential, the below recommendations should be followed:

Strong inhibitor

Initiation and dose-titration phase

- LLC: contraindicated
- AML: Day 1: 10 mg, Day 2: 20 mg. Day 3: 50 mg. Day 4: 100 mg or less

Fixed daily dose (after the dose titration phase: reduce the dose of venetoclax to 100 mg or less (or by at least 75% if already modified for other reasons).

Moderate CYP3A4 inhibitor

Reduce the dose of venetoclax by at least 50%. In CLL patients, avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medications or dose reduction as described [203].

Co-administration of venetoclax and posaconazole is contraindicated [62].

Patients should be monitored more closely for signs of toxic effects and further dose adjustment may be required. The dose of venetoclax used prior to initiating administration of a CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Venetoclax produced no effects on the QTc interval and there was no relationship between drug exposure and change in interval, even when administered at doses of 1200 mg [207].

Vinblastine. Vinblastine binds to tubulin and alters microtubule function, preventing polymerization and inducing depolymerization of the microtubules. It is metabolized by CYP3A4 and is a substrate of P-gp [208,209].

Vinblastine should be administered with caution in patients who are concomitantly taking drugs known to inhibit the metabolism of the drug through hepatic cytochrome CYP3A isoenzymes, or to patients with hepatic dysfunction. Concomitant administration of vinblastine and an inhibitor of this metabolic pathway may cause a more rapid onset and/or increased severity of side effects [209,210]. Concurrent use with itraconazole is contraindicated.

Vincristine. Vincristine sulfate affects cell mitosis by binding or crystallizing critical microtubular proteins of the mitotic spindle, such as tubulin, leading to arrest of cell division during metaphase and cell death. It is eliminated through CYP3A4 metabolism and is a P-gp substrate. It is indicated in the treatment of acute leukemia and malignant lymphomas, including Hodgkin's disease, non-Hodgkin's lymphomas (lymphocytic, mixed cell, histiocytic, undifferentiated, nodular and diffuse) [211].

Concomitant administration of vincristine sulfate with itraconazole or fluconazole (CYP3A4 inhibitors) has been associated with early onset and/or increased severity of neuromuscular adverse effects. Although there are no *in vivo* or *in vitro* studies, itraconazole, voriconazole, and posaconazole may increase plasma concentrations of vinca alkaloids, including vincristine sulfate, and may cause toxicity. Special caution should be exercised in patients under treatment with drugs that inhibit/induce hepatic metabolism by acting on cytochrome P450 isoenzymes, specifically in the CYP3A subfamily, or in patients with hepatic impairment [212–215]. It is recommended that dose titration of vincristine sulfate be considered. At present, no cases of toxicity related to the combination of vincristine with isavuconazole have been published.

CONCLUSIONS AND RECOMMENDATIONS

A review of the recommendations in Table 3 leads us to confirm the differences in potential for interactions among the various antifungals in relation to their inhibitory potency, especially of CYP3A4, and their ability to alter cardiac repolarization with the corresponding risk of prolonging electrocardiographic QT. Three drugs – itraconazole, voriconazole, and posaconazole – are relatively similar in promoting interactions with hematology-oncology drugs, relating to their ability to potently inhibit CYP3A4 and the added risk of prolonging QT. The remaining drug in this family, isavuconazole, has less in-

hibitory potency and no risk of QT prolongation. The latter is also a safer drug with fewer contraindications; it requires less vigilance and does not require monitoring of plasma levels for dose adjustment, as is recommended for the others. In addition, it can be used safely in patients with predisposing factors for QT prolongation [216–217].

CONFLICT OF INTEREST

JRA has received honoraria for talks on behalf of Pfizer, GSK, Menarini, Shionogi and MSD.

JB has received honoraria for talks on behalf of Pfizer, Gilead, Shionogi, and MSD.

LV has received honoraria for talks on behalf of Astellas, Gilead, MSD, Pfizer, Janssen, Astra Zeneca and GSK, and has received honoraria for consulting from Astellas, Gilead, Pfizer, and GSK

MK has received honoraria for lectures and consulting from Gilead, Jazz, Pfizer

LY has received honoraria for talks on behalf of Janssen, Abbvie, Gilead-Kite, Roche, Novartis, MSD, Pfizer, AstraZeneca, Novartis, Beigene, Lilly, has received honoraria for advisory board from Janssen, Abbvie, Gilead-Kite, Roche, Jazz, Sandoz, Celgene, MSD, Pfizer, AstraZeneca, BeiGene, Lilly, Alexion, and research funds from Janssen

JMA has been a consultant to and on the speakers bureau for Pfizer, Gilead, Merck Sharp and Dohme, and United Medical-Biotoscana.

IRC has received honoraria for talks on behalf of MSD, gilead, Astra Zeneca, Pfizer, GSK, Jansenn, and BMS and has received honoraria for advisory board from Pfizer, GSK, Astra Zeneca, and Gilead

JF has participated in scientific events or received remuneration in the form of research support or oral presentations from Merck, Pfizer, Gilead, MSD, Astellas, Novartis, and Roche.

MS has participated in advisory board or received honoraria for talks on behalf of Gilead, Menarini, MSD, Pfizer and Shionogi

CG received research support from Merck and Pfizer and honoraria for talks sponsored by Merck, Gilead, and Pfizer, and Shionogi.

CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Menarini, GSK and Sanofi, as well as a grant from Gilead Science, Pfizer, and GSK.

PG-S has participated in advisory board or received honoraria for talks on behalf of Pfizer, MSD, Gilead, Astellas, and Abbvie.

CDG has participated in advisory board or received honoraria for talks on behalf of MSD, Pfizer, Shionogi, Menarini, Gilead, Janssen, ViiV, Roche and GSK

Rest of authors have no conflict of interest.

REFERENCES

1. Chagas DF, Diniz LM, Lucas EA, Nogueira PSE. Disseminated fusariosis in a patient with bone marrow aplasia. An Bras Dermatol. 2020 Sep-Oct;95(5):609-614.
2. Forsythe A, Lewis G, Jordan R, Thompson GR 3rd. US database study: burden and healthcare resource utilization in adults with systemic endemic mycoses and aspergillosis. J Comp Eff Res. 2020 Jun;9(8):573-584.
3. Nucci M, Engelhardt M, Hamed K. Mucormycosis in South America: A review of 143 reported cases. Mycoses. 2019 Sep;62(9):730-738.
4. Singh S, Fatima Z, Hameed S. Predisposing factors endorsing Candida infections. Infez Med. 2015 Sep;23(3):211-23.
5. Ezeokoli OT, Gcilitshana O, Pohl CH. Risk Factors for Fungal Co-Infections in Critically Ill COVID-19 Patients, with a Focus on Immunosuppressants. J Fungi. (Basel) 2021 Jul 9;7(7):545.
6. McKinnon RA, Sorich MJ, Ward MB. Cytochrome P450, part 1: multiplicity and function. J Pharm Pract Re. 2008;38:55-7.
7. Venkatakrishnan K, Von Moltke LL, Greenblatt DJ. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. J Clin Pharmacol 2001;41: 1149–79.
8. Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet 2001;40:159–68.
9. Davidson MH. Does differing metabolism by cytochrome P450 have clinical importance? Curr Atheroscler Rep 2000;2:14–19.
10. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic- pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38:41–57.
11. Hall SD, Thummel KE, Watkins PB, et al. Molecular and physical mechanisms of first-pass extraction. Drug Metab Dispos 1999;27:161–6.
12. Liu X. Transporter-Mediated Drug-Drug Interactions and Their Significance. Adv Exp Med Biol. 2019;1141:241-291.
13. König J, Müller F, Fromm MF. Transporters and drug-drug interactions: important determinants of drug disposition and effects. Pharmacol Rev. 2013 May 17;65(3):944-66.
14. Deng J, Shao J, Markowitz JS, An G. ABC transporters in multi-drug resistance and ADME-Tox of small molecule tyrosine kinase inhibitors. Pharm Res. 2014 Sep;31(9):2237-55.
15. Pathan N, Shende P. Tailoring of P-glycoprotein for effective transportation of actives across blood-brain-barrier. J Control Release. 2021 Jul 10;335:398-407.
16. Huang L, Li B, Li X, Liu G, Liu R, Guo J, Xu B, Li Y, Fang W. Significance and Mechanisms of P-glycoprotein in Central Nervous System Diseases. Curr Drug Targets. 2019;20(11):1141-1155.
17. Lo A, Burckart GJ. P–glycoprotein and drug therapy in organ transplantation. J Clin Pharmacol 1999;39:995–1005.
18. Osowski CL, Dix SP, Lin LS, Mullins RE, Geller RB, Wingard JR. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. Transplantation 1996;61:1268–72.

19. Floren LC, Bekersky I, Benet LZ, Mekki Q, Dressler D, Lee JW, et al. Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. Clin Pharmacol Ther 1997;62:41–9.
20. Mañez R, Martin M, Raman V, Silverman D, Jain A, Warty V et al. Fluconazole therapy in transplant recipients receiving FK 506. Transplantation 1994;57:1521–3.
21. Tuteja S, Alloway RR, Johnson JA, Gaber AO. The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients. Transplantation 2001;71:1303–7.
22. Christians U, Jacobsen W, Benet LZ, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2002;41:813–51.
23. Husain A, Makadia V, Valicherla GR, Riyazuddin M, Gayen JR. Approaches to minimize the effects of P-glycoprotein in drug transport: A review. Drug Dev Res. 2022 Feb 1.
24. Murakami T, Bodor E, Bodor N. Factors and dosage formulations affecting the solubility and bioavailability of P-glycoprotein substrate drugs. Expert Opin Drug Metab Toxicol. 2021 May;17(5):555-580.
25. Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol. 2008 Jun 17;51(24):2291-300.
26. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Circulation. 2003 Apr 8;107(13):1764-9.
27. Albengres E, Le Louët H, Tillement JP. Systemic antifungal agents. Drug interactions of clinical significance. Drug Saf. 1998 Feb;18(2):83-97
28. Viskin S, Chorin E, Viskin D, Hochstadt A, Schwartz AL, Rosso R. Polymorphic Ventricular Tachycardia: Terminology, Mechanism, Diagnosis, and Emergency Therapy. Circulation. 2021 Sep 7;144(10):823-839.
29. Baracaldo- D, Llinás K, Corso JM, Restrepo CM, Dominguez CA, Fonseca DJ, et al Genetic and Molecular Aspects of Drug-Induced QT Interval Prolongation. Int J Mol Sci. 2021 Jul 28;22(15):8090.
30. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. Heart. 2022 Mar;108(5):332-338.
31. TeBay C, Hill AP, Windley MJ. Metabolic and electrolyte abnormalities as risk factors in drug-induced long QT syndrome. Biophys Rev. 2022 Jan 27:1-15.
32. Leong YH, Boast A, Cranswick N, Curtis N, Gwee A. Itraconazole Dosing and Drug Monitoring at a Tertiary Children's Hospital. Pediatr. Infect. Dis. J. 2019, 38, 60–64.
33. Itraconazole. (Oral Route) Proper Use—Mayo Clinic,. (n.d.) Available online: https://www.mayoclinic.org/drugs-supplements/ *(accessed on 2 November 2021)*(accessed on 2 November 2021)
34. Hurlé A.D.-G, Navarro, A.S, Sánchez, M.J.G. Therapeutic drug monitoring of itraconazole and the relevance of pharmacokinetic interactions. Clin. Microbiol. Infect. 2006, 12, 97–106.
35. Niwa T, Shiraga T, Takagi A. Effect of Antifungal Drugs on Cytochrome P450. (CYP) 2C9, CYP2C19, and CYP3A4 Activities in Human Liver Microsomes. Biol. Pharm. Bull. 2005, 28, 1805–1808.
36. Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE. Role of itraconazole metabolites in cyp3a4 inhibition. Drug Metab. Dispos. 2004, 32, 1121–1131.
37. Canadiol. (Itraconazol) Ficha técnica. AEMPS. Marzo 2022.
38. Kondo M, Kisanuki M, Kokawa Y, Gohara S, Kawano O, Kagiyama S, et al. Case Report: QT Prolongation and Abortive Sudden Death Observed in an 85-Year-Old Female Patient With Advanced Lung Cancer Treated With Tyrosine Kinase Inhibitor Osimertinib. Front Cardiovasc Med. 2021 Mar 19;8:655808.
39. Honig PK, Wortham DC, Hull R, Zamani K, Smith JE, Cantilena LR. Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. J Clin Pharmacol. 1993 Dec;33(12):1201-6.
40. NoorZurani MH, Vicknasingam B, Narayanan S. Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy. Drug Alcohol Rev. 2009 Nov;28(6):688-90.
41. Hoover CA, Carmichael JK, Nolan PE Jr, Marcus FI. Cardiac Arrest Associated With Combination Cisapride and Itraconazole Therapy. J Cardiovasc Pharmacol Ther. 1996 Jul;1(3):255-258.
42. Johnson, L.B.; Kauffman, C.A. Voriconazole: A New Triazole Antifungal Agent. Clin. Infect. Dis. 2003, 36, 630–637.
43. Vfend. (Voriconazol) Ficha técnica. AEMPS. Marzo 2022.
44. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet. 2006;45(7):649-63.
45. Geist MJ, Egerer G, Burhenne J, Riedel KD, Weiss J, Mikus G. Steady-state pharmacokinetics and metabolism of voriconazole in patients. J. Antimicrob. Chemother. 2013, 68, 2592–2599.
46. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole does not affect the steady-state pharmacokinetics of digoxin. Br J Clin Pharmacol. 2003 Dec;56 Suppl 1(Suppl 1):45-50.
47. Lempers VJ, van den Heuvel JJ, Russel FG, Aarnoutse RE, Burger DM, Brüggemann RJ, et al. Inhibitory Potential of Antifungal Drugs on ATP-Binding Cassette Transporters P-Glycoprotein, MRP1 to MRP5, BCRP, and BSEP. Antimicrob Agents Chemother. 2016 May 23;60(6):3372-9.
48. Li H, Li M, Yan J, Gao L, Zhou L, Wang Y, et al. Voriconazole therapeutic drug monitoring in critically ill patients improves efficacy and safety of antifungal therapy. Basic Clin Pharmacol Toxicol. 2020 Dec;127(6):495-504.
49. Luong ML, Al-Dabbagh M, Groll AH, Racil Z, Nannya Y, Mitsani D, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother. 2016 Jul;71(7):1786-99.
50. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet. 2002;41(12):913-58.
51. Blanco-Dorado S, Maroñas O, Latorre-Pellicer A, Rodríguez Jato MT, López-Vizcaíno A, Gómez Márquez A et al. Impact of CYP2C19 Genotype and Drug Interactions on Voriconazole Plasma Concentrations: A Spain Pharmacogenetic-Pharmacokinetic Prospective Multicenter Study. Pharmacother. J. Hum. Pharmacol. Drug Ther.

2019, 40, 17–25.

52. Geist MJ, Egerer G, Burhenne J, Mikus G. Safety of voriconazole in a patient with CYP2C9*2/CYP2C9*2 genotype. Antimicrob Agents Chemother. 2006 Sep;50(9):3227-8.
53. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009 May 15;48(10):1441-58.
54. Barreto JN, Cullen MW, Mara KC, Grove ME, Sierzchulski AG, Dahl NJ, et al. QT prolongation in patients with acute leukemia or high-risk myelodysplastic syndrome prescribed antifungal prophylaxis during chemotherapy-induced neutropenia. Leuk Lymphoma. 2019 Dec;60(14):3512-3520.
55. Pasternak Y, Shechter N, Loebstein R, Markovits N, Gueta I, Halkin H, et al. Voriconazole-induced QTc prolongation in a paediatric population. Acta Paediatr. 2019 Jun;108(6):1128-1132.
56. Brown JD, Lim LL, Koning S. Voriconazole associated torsades de pointes in two adult patients with haematological malignancies. Med Mycol Case Rep. 2014 Mar 13;4:23-5.
57. Elbey MA, Cil H, Onturk E, Islamoglu Y. OTc prolongation and torsade de pointes ventricular tachycardia in a small dose voriconazole therapy. Eur Rev Med Pharmacol Sci. 2012 Jan;16(1):100-2.
58. Philips JA, Marty FM, Stone RM, Koplan BA, Katz JT, Baden LR. Torsades de pointes associated with voriconazole use. Transpl Infect Dis. 2007 Mar;9(1):33-6.
59. Munayyer HK, Mann PA, Chau AS, Yarosh-Tomaine T, Greene JR, Hare RS, et al. Posaconazole is a potent inhibitor of sterol 14alpha-demethylation in yeasts and molds. Antimicrob Agents Chemother. 2004 Oct;48(10):3690-6.
60. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother. 2009 Mar;53(3):958-66.
61. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother. 2003 Sep;47(9):2788-95.
62. Noxafil. (Posaconazol) Ficha técnica. AEMPS. Marzo 2022.
63. Mian P, Trof RJ, Beishuizen A, Masselink JB, Cornet AD, Sportel ET. Suboptimal plasma concentrations with posaconazole suspension as prophylaxis in critically ill COVID-19 patients at risk of Covid-associated pulmonary aspergillosis. J Clin Pharm Ther. 2021 Aug 25.
64. Kraljevic M, Khanna N, Medinger M, Passweg J, Masouridi-Levrat S, Chalandon Y, et al. Swiss Transplant Cohort Study. Clinical considerations on posaconazole administration and therapeutic drug monitoring in allogeneic hematopoietic cell transplant recipients. Med Mycol. 2021 Jul 6;59(7):701-711.
65. Petitcollin A, Crochette R, Tron C, Verdier MC, Boglione-Kerrien C, Vigneau C, Bellissant E, Lemaitre F. Increased inhibition of cytochrome P450 3A4 with the tablet formulation of posaconazole. Drug Metab Pharmacokinet. 2016 Oct;31(5):389-393.
66. Shumaker AC, Bullard HM, Churpek J, Knoebel RW. Posaconazole-digoxin drug-drug interaction mediated by inhibition of P-glycoprotein. J Oncol Pharm Pract. 2019 Oct;25(7):1758-1761.
67. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharm Sci. 2004 Apr;21(5):645-53.
68. Panos G, Velissaris D, Karamouzos V, Matzaroglou C, Tylianakis M. Long QT Syndrome Leading to Multiple Cardiac Arrests After Posaconazole Administration in an Immune-Compromised Patient with Sepsis: An Unusual Case Report. Am J Case Rep. 2016 Apr 29;17:295-300.
69. Eiden C, Peyrière H, Tichit R, Cociglio M, Amedro P, Blayac JP, et al. Inherited long QT syndrome revealed by antifungals drug-drug interaction. J Clin Pharm Ther. 2007 Jun;32(3):321-4.
70. Poluzzi E, Raschi E, Motola D, Moretti U, De Ponti F. Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. Drug Saf. 2010 Apr 1;33(4):303-14.
71. Stelzer D, Weber A, Ihle F, Matthes S, Ceelen F, Zimmermann G, et al. Posaconazole liquid vs tablet formulation in lung transplant recipients. Mycoses. 2018 Mar;61(3):186-194.
72. Cresemba. (Isavuconazol) AEMPS. Ficha técnica. Marzo 2022
73. Warn, P.A.; Sharp, A.; Parmar, A.; Majithiya, J.; Denning, D.W.; Hope, W.W. Pharmacokinetics and Pharmacodynamics of a Novel Triazole, Isavuconazole: Mathematical Modeling, Importance of Tissue Concentrations, and Impact of Immune Status on Antifungal Effect. Antimicrob. Agents Chemother. 2009, 53, 3453–3461.
74. Pettit, N.N.; Carver, P.L. Isavuconazole. Ann. Pharmacother. 2015, 49, 825–842.
75. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi. (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016 Feb 20;387(10020):760-9.
76. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018 Apr 30;12:1033-1044.
77. Cojutti PG, Carnelutti A, Lazzarotto D, Sozio E, Candoni A, Fanin R, et al. Population Pharmacokinetics and Pharmacodynamic Target Attainment of Isavuconazole against Aspergillus fumigatus and Aspergillus flavus in Adult Patients with Invasive Fungal Diseases: Should Therapeutic Drug Monitoring for Isavuconazole Be Considered as Mandatory as for the Other Mold-Active Azoles? Pharmaceutics. 2021 Dec 6;13(12):2099.
78. Risum M, Vestergaard MB, Weinreich UM, Helleberg M, Vissing NH, Jørgensen R. Therapeutic Drug Monitoring of Isavuconazole: Serum Concentration Variability and Success Rates for Reaching Target in Comparison with Voriconazole. Antibiotics. (Basel) 2021 Apr 23;10(5):487.
79. Ellsworth M, Ostrosky-Zeichner L. Isavuconazole: Mechanism of Action, Clinical Efficacy, and Resistance. J Fungi. (Basel) 2020 Nov

29;6(4):324.

80. McCarthy MW, Moriyama B, Petraitiene R, Walsh TJ, Petraitis V. Clinical Pharmacokinetics and Pharmacodynamics of Isavuconazole. Clin Pharmacokinet. 2018 Dec;57(12):1483-1491.
81. Wilson DT, Dimondi VP, Johnson SW, Jones TM, Drew RH. Role of isavuconazole in the treatment of invasive fungal infections. Ther Clin Risk Manag. 2016 Aug 3;12:1197-206.
82. Groll AH, Desai A, Han D, Howieson C, Kato K, Akhtar S, et al. Pharmacokinetic Assessment of Drug-Drug Interactions of Isavuconazole With the Immunosuppressants Cyclosporine, Mycophenolic Acid, Prednisolone, Sirolimus, and Tacrolimus in Healthy Adults. Clin Pharmacol Drug Dev. 2017 Jan;6(1):76-85.
83. Yamazaki T, Desai A, Goldwater R, Han D, Lasseter KC, Howieson C, Akhtar S, Kowalski D, Lademacher C, Rammelsberg D, Townsend R. Pharmacokinetic Interactions Between Isavuconazole and the Drug Transporter Substrates Atorvastatin, Digoxin, Metformin, and Methotrexate in Healthy Subjects. Clin Pharmacol Drug Dev. 2017 Jan;6(1):66-75.
84. Keirns J, Desai A, Kowalski D, Lademacher C, Mujais S, Parker B, et al. QT Interval Shortening With Isavuconazole: In Vitro and In Vivo Effects on Cardiac Repolarization. Clin Pharmacol Ther. 2017 Jun;101(6):782-790.
85. Mellinghoff SC, Bassetti M, Dörfel D, Hagel S, Lehners N, Plis A, et al. Isavuconazole shortens the QTc interval. Mycoses. 2018 Apr;61(4):256-260.
86. Trang TP, Hanretty AM, Langelier C, Yang K. Use of isavuconazole in a patient with voriconazole-induced QTc prolongation. Transpl Infect Dis. 2017 Aug;19(4)
87. Calquence. (Acalabrutinib) Ficha técnica. AEMPS. Marzo 2022
88. Zhou D, Podoll T, Xu Y, Moorthy G, Vishwanathan K, Ware J, Slatter JG, Al-Huniti N. Evaluation of the Drug-Drug Interaction Potential of Acalabrutinib and Its Active Metabolite, ACP-5862, Using a Physiologically-Based Pharmacokinetic Modeling Approach. CPT Pharmacometrics Syst Pharmacol. 2019 Jul;8(7):489-499.
89. Chen B, Zhou D, Wei H, Yotvat M, Zhou L, Cheung J, et al. Acalabrutinib CYP3A mediated Drug-Drug Interactions: Clinical Evaluations and Physiologically-Based Pharmacokinetic Modeling to inform dose adjustment strategy. Br J Clin Pharmacol. 2022 Feb 15.
90 Velcade. (Bortezomid) Ficha técnica. AEMPS. Marazo 2022.
91. Venkatakrishnan K, Rader M, Ramanathan RK, Ramalingam S, Chen E, Riordan W, et al. Effect of the CYP3A inhibitor ketoconazole on the pharmacokinetics and pharmacodynamics of bortezomib in patients with advanced solid tumors: a prospective, multicenter, open-label, randomized, two-way crossover drug-drug interaction study. Clin Ther. 2009;31 Pt 2:2444-58.
92. Koda Y, Mori T, Shimizu T, Kato J, Yamane A, Sadahira K, Tsukada Y, Yokoyama K, Hashimoto N, Hattori Y, Okamoto S. (Early onset of paralytic ileus caused by simultaneous administration of bortezomib and azole antifungals in multiple myeloma patients]. Rinsho Ketsueki. 2012 Aug;53(8):760-4.
93. Jung SH, Kang SJ, Jang HC, Ahn JS, Yang DH, Lee SS, et al. Effect of levofloxacin prophylaxis for prevention of severe infections in multiple myeloma patients receiving bortezomib-containing regimens. Int J Hematol. 2014 Nov;100(5):473-7.
94. Bosulif. (Bosutinib) Ficha técnica. AEMPS. Marzo 2022.
95. Abbas R, Hug BA, Leister C, Burns J, Sonnichsen D. Effect of ketoconazole on the pharmacokinetics of oral bosutinib in healthy subjects. J Clin Pharmacol. 2011 Dec;51(12):1721-7.
96. Hsyu PH, Pignataro DS, Matschke K. Effect of aprepitant, a moderate CYP3A4 inhibitor, on bosutinib exposure in healthy subjects. Eur J Clin Pharmacol. 2017 Jan;73(1):49-56.
97. Abbas R, Hug BA, Leister C, Sunnitises D. A randomized, crossover, placebo- and moxifloxacin-controlled study to evaluate the effects of bosutinib. (SKI-606), a dual Src/Abl tyrosine kinase inhibitor, on cardiac repolarization in healthy adult subjects. Int J Cancer. 2012 Aug 1;131(3):E304-11.
98. Abbas R, Chalon S, Leister C, El Gaaloul M, Sonnichsen D. Evaluation of the pharmacokinetics and safety of bosutinib in patients with chronic hepatic impairment and matched healthy subjects. Cancer Chemother Pharmacol. 2013 Jan;71(1):123-32.
99. Cortes JE, Jean Khoury H, Kantarjian H, Brümmendorf TH, Mauro MJ, Matczak E, et al. Long-term evaluation of cardiac and vascular toxicity in patients with Philadelphia chromosome-positive leukemias treated with bosutinib. Am J Hematol. 2016 Jun;91(6):606-16.
100. Kyprolis. (Carfilzomib) Ficha técnica. AEMPS. Marzo 2022.
101. Zhai Y, Ye X, Hu F, Xu J, Guo X, Cao Y, et al. Cardiovascular Toxicity of Carfilzomib: The Real-World Evidence Based on the Adverse Event Reporting System Database of the FDA, the United States. Front Cardiovasc Med. 2021 Sep 27;8:735466.
102. Genoxal. (Ciclofosfamida) Ficha técnica. AEMPS. Marzo 2022.
103. Cai T, Liao Y, Chen Z, Zhu Y, Qiu X. The Influence of Different Triazole Antifungal Agents on the Pharmacokinetics of Cyclophosphamide. Ann Pharmacother. 2020 Jul;54(7):676-683.
104. Shibata Y, Tamemoto Y, Singh SP, Yoshitomo A, Hozuki S, Sato H, Hisaka A. Plausible drug interaction between cyclophosphamide and voriconazole via inhibition of CYP2B6. Drug Metab Pharmacokinet. 2021 Aug;39:100396.
105. Sebastian KK, Alzayer H, Abraham E, Roche D, Reddan D, Lappin D. Cutaneous Absidia corymbifera in a Lupus Nephritis Patient. Cureus. 2021 Nov 12;13(11):e19512.
106. Nakamae H, Tsumura K, Hino M, Hayashi T, Tatsumi N. QT dispersion as a predictor of acute heart failure after high-dose cyclophosphamide. Lancet. 2000 Mar 4;355(9206):805-6.
107. Sandimmun neoral. (Ciclosporina) Ficha técnica. AEMPS. Marzo 2022
108. Shaw MA, Gumbleton M, Nicholls PJ. Interaction of cyclosporin and itraconazole. Lancet. 1987 Sep 12;2(8559):637. doi: 10.1016/s0140-6736(87)93038-8.
109. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporin. An update. Clin Pharmacokinet. 1996 Feb;30(2):141-79.
110. Gomez DY, Wacher VJ, Tomlanovich SJ, Hebert MF, Benet LZ. The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. Clin Pharmacol Ther. 1995 Jul;58(1):15-9.

111. Groll AH, Townsend R, Desai A, Azie N, Jones M, Engelhardt M, Schmitt-Hoffman AH, Brüggemann RJM. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. Transpl Infect Dis. 2017 Oct;19(5)

112. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010 Aug;30(8):842-54.

113. Gu TM, Lewis JS 2nd, Le H, Bubalo JS. Comparative effects of fluconazole, posaconazole, and isavuconazole upon tacrolimus and cyclosporine serum concentrations. J Oncol Pharm Pract. 2021 Jul 1:10781552211029046.

114. Decembrino N, Perruccio K, Zecca M, Colombini A, Calore E, Muggeo P, et al. A Case Series and Literature Review of Isavuconazole Use in Pediatric Patients with Hemato-oncologic Diseases and Hematopoietic Stem Cell Transplantation. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e01783-19.

115. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy. 2007 Jun;27(6):825-34.

116. Sprycel. (Dasatinib) Ficha técnica. AEMPs. Marzo 2022.

117. Johnson FM, Agrawal S, Burris H, Rosen L, Dhillon N, Hong D, et al. Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. Cancer. 2010 Mar 15;116(6):1582-91.

118. Cirmi S, El Abd A, Letinier L, Navarra M, Salvo F. Cardiovascular Toxicity of Tyrosine Kinase Inhibitors Used in Chronic Myeloid Leukemia: An Analysis of the FDA Adverse Event Reporting System Database. (FAERS) Cancers. (Basel) 2020 Mar 30;12(4):826.

119. Redner RL, Beumer JH, Kropf P, Agha M, Boyiadzis M, Dorritie K, et al. A phase-1 study of dasatinib plus all-trans retinoic acid in acute myeloid leukemia. Leuk Lymphoma. 2018 Nov;59(11):2595-2601.

120. Farmiblastina. (Doxorubicina) Ficha técnica. AEMPS. Marzo 2022)

121. Millikan R, Baez L, Banerjee T, Wade J, Edwards K, Winn R, Smith TL, Logothetis C. Randomized phase 2 trial of ketoconazole and ketoconazole/doxorubicin in androgen independent prostate cancer. Urol Oncol. 2001 May;6(3):111-115.

122. Copiktra. (Duvelisib) Ficha técnica. AEMPS Marzo 2022.

123. Etopósido EFG. (Etopósido) Ficha técnica. AEMPS. Marzo 2022.

124. Yong WP, Desai AA, Innocenti F, Ramirez J, Shepard D, Kobayashi K, et al. Pharmacokinetic modulation of oral etoposide by ketoconazole in patients with advanced cancer. Cancer Chemother Pharmacol. 2007 Nov;60(6):811-9.

125. Xospata. (Gilteritinib) Ficha técnica. AEMPS. Marzo 2022.

126. James AJ, Smith CC, Litzow M, Perl AE, Altman JK, Shepard D, et al. Pharmacokinetic Profile of Gilteritinib: A Novel FLT-3 Tyrosine Kinase Inhibitor. Clin Pharmacokinet. 2020 Oct;59(10):1273-1290.

127. Kang C, Blair HA. Gilteritinib: A Review in Relapsed or Refractory FLT3-Mutated Acute Myeloid Leukaemia. Target Oncol. 2020 Oct;15(5):681-689.

128. Daurismo. (Gasdegib) Ficha técnica. AEMPS. Marzo 2022.

129. Shaik MN, LaBadie RR, Rudin D, Levin WJ. Evaluation of the effect of food and ketoconazole on the pharmacokinetics of the smoothened inhibitor PF-04449913 in healthy volunteers. Cancer Chemother Pharmacol. 2014 Aug;74(2):411-8.

130. Norsworthy KJ, By K, Subramaniam S, Zhuang L, Del Valle PL, Przepiorka D, et al. FDA Approval Summary: Glasdegib for Newly Diagnosed Acute Myeloid Leukemia. Clin Cancer Res. 2019 Oct 15;25(20):6021-6025.

131. Imbruvica. (Ibrutinib) Ficha técnica. AEMPS. Marzo 2022.

132. Tapaninen, T.; Olkkola, A.M.; Tornio, A.; Neuvonen, M.; Elonen, E.; Neuvonen, P.J.; et al. Itraconazole Increases Ibrutinib Exposure 10-Fold and Reduces Interindividual Variation—A Potentially Beneficial Drug-Drug Interaction. Clin. Transl. Sci. **2019**, 13, 345–351.

133. de Jong J, Skee D, Murphy J, Sukbuntherng J, Hellemans P, Smit J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. Pharmacol Res Perspect. 2015 Aug;3(4):e00156.

134. de Jong J, Hellemans P, De Wilde S, Patricia D, Masterson T, Manikhas G, et al. A drug-drug interaction study of ibrutinib with moderate/strong CYP3A inhibitors in patients with B-cell malignancies. Leuk Lymphoma. 2018 Dec;59(12):2888-2895.

135. Cummins KC, Cheng MP, Kubiak DW. Isavuconazole for the treatment of invasive fungal disease in patients receiving ibrutinib. Leuk Lymphoma. 2018 Jul 24:1-4.

136. de Jong J, Hellemans P, Jiao JJ, Huang Y, Mesens S, Sukbuntherng J, et al. Ibrutinib does not prolong the corrected QT interval in healthy subjects: results from a thorough QT study. Cancer Chemother Pharmacol. 2017 Dec;80(6):1227-1237.

137. Zydelig. (Idelalisib) Ficha técnica. AEMPS. Marzo 2022.

138. Ramanathan S, Jin F, Sharma S, Kearney BP. Clinical Pharmacokinetic and Pharmacodynamic Profile of Idelalisib. Clin Pharmacokinet. 2016 Jan;55(1):33-45.

139. Glivec. (Imatinib) Ficha técnica. AEMPS. Marzo 2022.

140. Lin Q, Xie S, Qiu X, Chen J, Xu RA. Drug-drug interaction study of imatinib and voriconazole in vitro and in vivo. Infect Drug Resist. 2019 Apr 30;12:1021-1027.

141. Gambillara E, Laffitte E, Widmer N, Decosterd LA, Duchosal MA, Kovacsovics T, Panizzon RG. Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukemia. Dermatology. 2005;211(4):363-5.

142. Porta-Sánchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, Thavendiranathan P. Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review. J Am Heart Assoc. 2017 Dec 7;6(12):e007724.

143. Revlimid. (Lenlidomida) Fciha técnica. AEMPS. Marzo 2022

144. Chen N, Weiss D, Reyes J, Liu L, Kasserra C, Wang X, et al No clinically significant drug interactions between lenalidomide and Pglycoprotein substrates and inhibitors: results from controlled phase I studies in healthy volunteers. Cancer Chemother Pharmacol. 2014 May;73(5):1031-9.

145. Ogura M, Imaizumi Y, Uike N, Asou N, Utsunomiya A, Uchida T, et al. Lenalidomide in relapsed adult T-cell leukaemia-lymphoma or peripheral T-cell lymphoma. (ATLL-001): a phase 1, multicentre,

dose-escalation study. Lancet Haematol. 2016 Mar;3(3):e107-18.

146. Chen N, Ye Y, Liu L, Reyes J, Assaf MS, Kasserra C, et al. Lenalidomide at therapeutic and supratherapeutic doses does not prolong QTc intervals in the thorough QTc study conducted in healthy men. Basic Clin Pharmacol Toxicol. 2013 Sep;113(3):179-86.
147. Rydapt. (Midastaurina) EPAR. EMA Marzo 2022.
148. Dutreix C, Munarini F, Lorenzo S, Roesel J, Wang Y. Investigation into CYP3A4-mediated drug-drug interactions on midostaurin in healthy volunteers. Cancer Chemother Pharmacol. 2013 Dec;72(6):1223-34.
149. Menna P, Salvatorelli E, Del Principe MI, Perrone S, Pagano L, Marchesi F, Minotti G. Choosing Antifungals for the Midostaurin-Treated Patient: Does CYP3A4 Outweigh Recommendations? A Brief Insight from Real Life. Chemotherapy. 2021;66(1-2):47-52.
150. Perrone S, Lisi C, La Barbera EO, Luise C, Lichtner M, Girmenia C, Cimino G. Isavuconazole Therapy of Disseminated and Encephalic Saprochaete Capitata Infection in an Acute Myeloid Leukemia Patient Treated with Midostaurin. Mediterr J Hematol Infect Dis. 2020 May 1;12(1):e2020026.
151. Tollkuci E. Isavuconazole therapy in an FLT3 mutated acute myeloid leukemia patient receiving midostaurin: A case report. J Oncol Pharm Pract. 2019 Jun;25(4):987-989.
152. del Corral A, Dutreix C, Huntsman-Labed A, Lorenzo S, Morganroth J, Harrell R, et al. Midostaurin does not prolong cardiac repolarization defined in a thorough electrocardiogram trial in healthy volunteers. Cancer Chemother Pharmacol. 2012 May;69(5):1255-63.
153. Tasigna. (Nilotinib) Ficha técnica. AEMPS. Marzo 2022.
154. Tanaka C, Yin OQ, Smith T, Sethuraman V, Grouss K, Galitz L, et al. Effects of rifampin and ketoconazole on the pharmacokinetics of nilotinib in healthy participants. J Clin Pharmacol. 2011 Jan;51(1):75-83.
155. Singh R, Kapoor J, Ahmed R, Mehta P, Khushoo V, Agrawal P, et al. A Retrospective Cohort Study of Upfront Nilotinib in Chronic Myeloid Leukemia: A Single-Center Experience. South Asian J Cancer. 2021 Nov 24;10(4):246-250.
156. Kim TD, le Coutre P, Schwarz M, Grille P, Levitin M, Fateh-Moghadam S, et al. Clinical cardiac safety profile of nilotinib. Haematologica. 2012 Jun;97(6):883-9.
157. Oxaliplatino EFG. (Oxaliplatino) Ficha técnica. AEMPS. Marzo 2022
158. Hancox JC, Caves RE, Choisy SC, James AF. QT interval prolongation and torsades de pointes with oxaliplatin. Ther Adv Drug Saf. 2016 Dec;7(6):261-263.
159. Chang RY, Lee MY, Kan CB, Hsu WP, Hsiao PC. Oxaliplatin-induced acquired long QT syndrome with torsades de pointes and myocardial injury in a patient with dilated cardiomyopathy and rectal cancer. J Chin Med Assoc. 2013 Aug;76(8):466-9.
160. Imnovid. (Pomalidomida) Ficha técnica. AEMPS. Marzo 2022
161. Kasserra C, Assaf M, Hoffmann M, Li Y, Liu L, Wang X, Kumar G, Palmisano M. Pomalidomide: evaluation of cytochrome P450 and transporter-mediated drug-drug interaction potential in vitro and in healthy subjects. J Clin Pharmacol. 2015 Feb;55(2):168-78.
162. Mondal SA, Assaf M, Liu L, O'Mara E. A Phase 1, double-blind, 4-period crossover study to investigate the effects of pomalidomide on QT interval in healthy male subjects. Cancer Chemother Pharmacol. 2016 Feb;77(2):251-8.
163. Iclusig. (Ponatinib) Ficha técnica. AEMPS. Marzo 2022
164. Narasimhan NI, Dorer DJ, Niland K, Haluska F, Sonnichsen D. Effects of ketoconazole on the pharmacokinetics of ponatinib in healthy subjects. J Clin Pharmacol. 2013 Sep;53(9):974-81.
165. Sonnichsen D, Dorer DJ, Cortes J, Talpaz M, Deininger MW, Shah NP, et al. Analysis of the potential effect of ponatinib on the QTc interval in patients with refractory hematological malignancies. Cancer Chemother Pharmacol. 2013 Jun;71(6):1599-607.
166. Jeng S, Chanchairujira T, Jusko W, Steiner R. Prednisone metabolism in recipients of kidney or liver transplants and in lung recipients receiving ketoconazole. Transplantation. 2003 Mar 27;75(6):792-5.
167. Prednisona EFG. (Prednisona) Ficha técnica. AEMPS. Marzo 2022.
168. Jakavi. (Ruxolitinib) Ficha técnica. AEMPS. Marzo 2022.
169. Shi JG, Chen X, Emm T, Scherle PA, McGee RF, Lo Y, et al. The effect of CYP3A4 inhibition or induction on the pharmacokinetics and pharmacodynamics of orally administered ruxolitinib. (INCB018424 phosphate) in healthy volunteers. J Clin Pharmacol. 2012 Jun;52(6):809-18.
170. Aslanis V, Umehara K, Huth F, Ouatas T, Bharathy S, Butler AA, Zhou W, Gadbaw B. Multiple administrations of fluconazole increase plasma exposure to ruxolitinib in healthy adult subjects. Cancer Chemother Pharmacol. 2019 Oct;84(4):749-757.
171. Hirano A, Yamasaki M, Saito N, Iwato K, Daido W, Funaishi K, et al. Pulmonary cryptococcosis in a ruxolitinib-treated patient with primary myelofibrosis. Respir Med Case Rep. 2017 Jul 4;22:87-90.
172. Punwani N, Yeleswaram S, Chen X, Bowman J, Soloviev M, Williams W. Evaluation of the effect of ruxolitinib on cardiac repolarization: A thorough QT study. Clin Pharmacol Drug Dev. 2014 May;3(3):207-14.
173. Nexpovio. (Selinexor) Ficha técnica. AEMPS. Marzo 2022
174. Li SL, Zhang Y, Cheng QS, Xin JZ, Dong ZQ, Qiu XJ. UPLC-MS/MS Measurement of the Effect of Isavuconazole, Itraconazole and Fluconazole on the Pharmacokinetics of Selinexor in Rats. Infect Drug Resist. 2020 Sep 14;13:3153-3161.
175. Rapamune. (Sirolimus) Ficha técnica. AEMPS. Marzo 2022.
176. Thomas PP, Manivannan J, John GT, Jacob CK. Sirolimus and ketoconazole co-prescription in renal transplant recipients. Transplantation. 2004 Feb 15;77(3):474-5.
177. Surowiec D, DePestel DD, Carver PL. Concurrent administration of sirolimus and voriconazole: a pilot study assessing safety and approaches to appropriate management. Pharmacotherapy. 2008 Jun;28(6):719-29.
178. Ceberio I, Dai K, Devlin SM, Barker JN, Castro-Malaspina H, Goldberg JD, et al. Safety of voriconazole and sirolimus coadministration after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2015 Mar;50(3):438-43.
179. Cho E, Chan H, Nguyen HM, Shayani S, Nakamura R, Pon D. Management of drug interaction between posaconazole and sirolimus in

patients who undergo hematopoietic stem cell transplant. Pharmacotherapy. 2015 Jun;35(6):578-85.

180. Petitcollin A, Crochette R, Tron C, Verdier MC, Boglione-Kerrien C, Vigneau C, et al. Increased inhibition of cytochrome P450 3A4 with the tablet formulation of posaconazole. Drug Metab Pharmacokinet. 2016 Oct;31(5):389-393.
181. Kieu V, Jhangiani K, Dadwal S, Nakamura R, Pon D. Effect of isavuconazole on tacrolimus and sirolimus serum concentrations in allogeneic hematopoietic stem cell transplant patients: A drug-drug interaction study. Transpl Infect Dis. 2019 Feb;21(1):e13007.
182. Prograf. (Tacrolimus) Ficha técnica. AEMPS. Marzo 2022.
183. Mori T, Kato J, Yamane A, Sakurai M, Kohashi S, Kikuchi T, et al. Drug interaction between voriconazole and tacrolimus and its association with the bioavailability of oral voriconazole in recipients of allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2012 May;95(5):564-9.
184. Spriet I, Grootaert V, Meyfroidt G, Debaveye Y, Willems L. Switching from intravenous to oral tacrolimus and voriconazole leads to a more pronounced drug-drug interaction. Eur J Clin Pharmacol. 2013 Mar;69(3):737-8.
185. Trifilio SM, Scheetz MH, Pi J, Mehta J. Tacrolimus use in adult allogeneic stem cell transplant recipients receiving voriconazole: preemptive dose modification and therapeutic drug monitoring. Bone Marrow Transplant. 2010 Aug;45(8):1352-6.
186. Chanoine S, Gautier-Veyret E, Pluchart H, Tonini J, Fonrose X, et al. Tablets or oral suspension for posaconazole in lung transplant recipients? Consequences for trough concentrations of tacrolimus and everolimus. Br J Clin Pharmacol. 2021 Feb;87(2):427-435.
187. Collins J, Shea K, Parsad S, Plach K, Lee P. The impact of initiating posaconazole on tacrolimus pharmacokinetics in allogeneic stem cell transplantation. J Oncol Pharm Pract. 2020 Jan;26(1):5-12.
188. Fu C, Chen J, Xu Y, Wu D. Dose adjustment of immunosuppressants during co-administration of posaconazole: a systematic review. Clin Invest Med. 2018 Mar 27;41(1):E5-E15.
189. Kufel WD, Armistead PM, Daniels LM, Ptachcinski JR, Alexander MD, Shaw JR. Drug-Drug Interaction Between Isavuconazole and Tacrolimus: Is Empiric Dose Adjustment Necessary? J Pharm Pract. 2020 Apr;33(2):226-230.
190. Trifilio S, Rubin H, Monacelli A, Mehta J. Tacrolimus dose modification in patients receiving concomitant isavuconazole after hematopoietic stem cell transplantation. J Oncol Pharm Pract. 2021 Jun;27(4):857-862.
191. Rivosecchi RM, Clancy CJ, Shields RK, Ensor CR, Shullo MA, Falcione BA, et al. Effects of Isavuconazole on the Plasma Concentrations of Tacrolimus among Solid-Organ Transplant Patients. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00970-17.
192. Gu TM, Lewis JS 2nd, Le H, Bubalo JS. Comparative effects of fluconazole, posaconazole, and isavuconazole upon tacrolimus and cyclosporine serum concentrations. J Oncol Pharm Pract. 2021 Jul 1:10781552211029046.
193. Burger CI, Clase CM, Gangji AS. Case report: drug interaction between tacrolimus and amiodarone with QT prolongation. Transplantation. 2010 May 15;89(9):1166-7.
194. Gerhardt U, Suwelack B, Pawolka A, Hohage H. High QT dispersion in tacrolimus-treated kidney transplant recipients. Transplant Proc. 2001 May;33(3):2148-50.
195. Vesanoid. (Tretinoína o ácido transretinoico, ATRA)
196. Afacan Ozturk HB, Albayrak M, Maral S, Reis Aras M, Yilmaz F, Akyol P, et al. Hypercalcemia associated with the interaction between all trans retinoic acid and posaconazole in an acute promyelocytic leukemia case. J Oncol Pharm Pract. 2021 Dec;27(8):2027-2029.
197. Hashmi Y, Memon SF, Khan YA, Jabbar N, Mansoor N. The Effects of Voriconazole on Metabolism of All-Trans Retinoic Acid in the Treatment of Acute Promyelocytic Leukemia: A Case Report. Cureus. 2021 Feb 14;13(2):e13337.
198. Lancet JE, Moseley AB, Coutre SE, DeAngelo DJ, Othus M, et al. A phase 2 study of ATRA, arsenic trioxide, and gemtuzumab ozogamicin in patients with high-risk APL. (SWOG 0535) Blood Adv. 2020 Apr 28;4(8):1683-1689.
199. Trisenox. (Trióxido de arsénico) Ficha técnica. AEMPS. Marzo 2022.
200. Zeitjian V, Moazez C, Arslan W, Saririan M. QT Independent Ventricular Tachycardia Induced by Arsenic Trioxide. Case Rep Cardiol. 2019 Oct 13;2019:9870283.
201. Jiang Y, Du W, Chu Q, Qin Y, Tuguzbaeva G, Wang H, et al. Downregulation of Long Non-Coding RNA Kcnq1ot1: An Important Mechanism of Arsenic Trioxide-Induced Long QT Syndrome. Cell Physiol Biochem. 2018;45(1):192-202.
202. Roboz GJ, Ritchie EK, Carlin RF, Samuel M, Gale L, Provenzano-Gober JL, et al. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. J Clin Oncol. 2014 Nov 20;32(33):3723-8.
203. Venclyxto. (Venetoclax) Ficha técnica. AEMPS. Marzo 2022. Venclyxto
204. Agarwal SK, Salem AH, Danilov AV, Hu B, Puvvada S, Gutierrez M, et al. Effect of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of venetoclax, a BCL-2 inhibitor, in patients with non-Hodgkin lymphoma. Br J Clin Pharmacol. 2017 Apr;83(4):846-854.
205 Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, et al. Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. Clin Ther. 2017 Feb;39(2):359-367.
206. Bose P, McCue D, Wurster S, Wiederhold NP, Konopleva M, Kadia TM, Borthakur G, et al. Isavuconazole as Primary Antifungal Prophylaxis in Patients With Acute Myeloid Leukemia or Myelodysplastic Syndrome: An Open-label, Prospective, Phase 2 Study. Clin Infect Dis. 2021 May 18;72(10):1755-1763.
207. Freise KJ, Dunbar M, Jones AK, Hoffman D, Enschede SL, Wong S, et al. Venetoclax does not prolong the QT interval in patients with hematological malignancies: an exposure-response analysis. Cancer Chemother Pharmacol. 2016 Oct;78(4):847-53.
208. Vinblastina EFG. (Vinblastina) Ficha técnica. AEMPS. Marzo 2022
209. Zhou-Pan XR, Sérée E, Zhou XJ, Placidi M, Maurel P, Barra Y, et al. Involvement of human liver cytochrome P450 3A in vinblastine metabolism: drug interactions. Cancer Res. 1993 Nov 1;53(21):5121-6.

210. Ohnishi A, Matsuo H, Yamada S, Takanaga H, Morimoto S, Shoyama Y, et al. Effect of furanocoumarin derivatives in grapefruit juice on the uptake of vinblastine by Caco-2 cells and on the activity of cytochrome P450 3A4. Br J Pharmacol. 2000 Jul;130(6):1369-77.

211. Vincristina. Ficha técnica. AEMPS. Marzo 2022.

212. Foroughinia F, Baniasadi S, Seifi S, Fahimi F. Vincristine-induced seizure potentiated by itraconazole following RCHOP chemotherapy for diffuse large B-cell lymphoma. Curr Drug Saf. 2012 Nov 1;7(5):372-4.

213. Madsen ML, Due H, Ejskjær N, Jensen P, Madsen J, Dybkær K. Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. Cancer Chemother Pharmacol. 2019 Sep;84(3):471-485.

214. Lin MJ, Paul MR, Kuo DJ. Severe Neuropathic Pain With Concomitant Administration of Vincristine and Posaconazole. J Pediatr Pharmacol Ther. 2018 Sep-Oct;23(5):417-420.

215. Pekpak E, İleri T, İnce E, Ertem M, Uysal Z. Toxicity of Vincristine Combined With Posaconazole in Children With Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2018 Jul;40(5):e309-e310.

216. Brüggemann RJ, Verheggen R, Boerrigter E, Stanzani M, Verweij PE, Blijlevens NMA, Lewis RE. Management of drug-drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs. Lancet Haematol. 2022 Jan;9(1):e58-e72.

217. Megías-Vericat JE, Solana-Altabella A, Ballesta-López O, Martínez-Cuadrón D, Montesinos P. Drug-drug interactions of newly approved small molecule inhibitors for acute myeloid leukemia. Ann Hematol. 2020 Sep;99(9):1989-2007.

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Mycoplasma pneumoniae y resistencias a macrólidos: ¿Conocemos la situación en Europa?

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RESUMEN

Mycoplasma pneumoniae es una bacteria que carece de pared celular. Produce infecciones en todo el mundo, en brotes epidémicos cada 4-7 años, o en forma endémica. Sus manifestaciones clínicas se producen mayoritariamente en el tracto respiratorio y es una causa común de neumonía atípica. El tratamiento se realiza con macrólidos, tetraciclinas o fluoroquinolonas. Desde el año 2000 se ha detectado un aumento de resistencias a macrólidos a nivel mundial, siendo más frecuentes en Asia. En Europa la frecuencia de resistencias oscila entre el 1% y 25% en diferentes países. La combinación de técnicas moleculares y serológicas aporta una alta sensibilidad en la confirmación diagnóstica, siendo de gran utilidad para la detección y control de brotes de *M. pneumoniae*. La detección de resistencia a macrólidos requiere una técnica de secuenciación.

Palabras clave: *Mycoplasma pneumoniae*. Resistencias macrólidos. PCR

Macrolide-resistant *Mycoplasma pneumoniae*: Do we know the situation in Europe?

ABSTRACT

Mycoplasma pneumoniae is a bacterium that lacks a cell wall. It produces infections all It produces infections worldwide, in epidemic outbreaks every 4-7 years, or endemically. Its clinical manifestations occur mostly in the respiratory tract and it is a common cause of atypical pneumonia. The treatment is with macrolides, tetracyclines or fluoroquinolones. Since 2000, an increase in resistance to macrolides has been detected worldwide, being more frequent in Asia. In Europe the frequency of resistance ranges between 1% and 25%, depending on the country. Molecular techniques and serology techniques provides very high sensitivity in diagnostic confirmation, being very useful for detecting and controlling *M. pneumoniae* outbreaks. The detection of resistance to macrolides requires a sequencing technique.

Keywords: *Mycoplasma pneumoniae*, resistance, macrolides, PCR

INTRODUCCIÓN

Mycoplasma pneumoniae es una bacteria intracelular que fue descubierta en 1944 por Eaton, cuando cultivó una expectoración de un paciente con neumonía primaria de características atípicas. En 1963 se propuso su denominación taxonómica [1].

M. pneumoniae es una bacteria muy evolucionada, con propiedades y características especiales, siendo las principales: la carencia de pared, su pequeño genoma y especiales exigencias nutricionales. La falta de pared celular hace que no se tiña con Gram, que tenga resistencia a antibióticos betalactámicos y elevada sensibilidad a variaciones de ph, temperatura, tensión osmótica y detergentes. Sus exigencias nutricionales hacen que sea una bacteria difícil de cultivar en el laboratorio.

Es uno de los agentes etiológicos de las llamadas "neumonías atípicas". Este término surgió a comienzos de 1940, tras el inicio de la era antibiótica, y define a aquella neumonía que se asocian con clínica extra-pulmonar, presenta patrón radiológico parcheado o intersticial en la radiografía de tórax, no se identifica el agente causal en tinción de Gram o cultivo de esputo convencional y no responden a antibióticos betalactámicos [2]. La incidencia de *M. pneumoniae* resistente a los macrólidos varía a nivel mundial, y el este de Asia tiene un mayor grado de resistencia. Sin embargo, también se requiere atención en otras áreas, y se deben considerar alternativas a los antibióticos para el tratamiento en países con alta prevalencia [3].

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PATOGENIA

Al microscopio electrónico, tiene forma de botella y destaca un extremo afilado especial o "tip" por el que se adhiere a las células epiteliales. Esta estructura de anclaje está formada por un sistema complejo de proteínas, siendo la principal la adhesina P_1, que regula la interacción con las células del aparato respiratorio, y puede lesionar las células de dicho epitelio y su actividad ciliar. Esta proteína también es la diana de los principales anticuerpos que produce la respuesta inmunitaria del huésped [4]. La falta de pared celular de *M. pneumoniae* y el estrecho contacto con la membrana de la célula huésped facilita el intercambio de compuestos que son importantes para su crecimiento y proliferación. La bacteria también tiene citotoxinas, siendo la más importante la toxina CARDS (por su acrónimo inglés community-acquired respiratory distress syndrome) que puede promover células pro- inflamatorias que dan lugar a células y citocinas inflamatorias que son capaces de lesionar al huésped, entre ellas destaca la interleucina 8, potente quimiocina para neutrófilos [4].

M. pneumomiae actúa principalmente en la superficie de células epiteliales respiratorias, pero puede invadir otros tejidos y replicarse intracelularmente. Las manifestaciones clínicas debidas a la infección aguda y las manifestaciones extrapulmonares son además el resultado de los efectos inmunopatológicos e inflamatorios producidos por el huésped. Diversas lipoproteínas de superficie de la célula huésped estimulan la interleucina 6, factor de necrosis tumoral alfa, así como infiltración de neutrófilos. Se estimulan los macrófagos, migran al sitio de infección después de opsonización de *M. pneumoniae* por parte de anticuerpos o complemento y posteriormente se produce la infiltración de neutrófilos, linfocitos B y T (CD4+). Se ha descrito que la endocitosis de esta bacteria por parte de la célula huésped, podría ayudar a que se establezca un estado de enfermedad latente o crónica, y esto puede facilitar que *M. pneumoniae* evada la respuesta inmune e interfiera la eficacia de algunos antibióticos [5].

Los macrólidos, antibióticos más utilizados frente a este microorganismo, actúan inhibiendo la síntesis de proteínas sobre la subunidad ribosómica 50S y se unen a los nucleótidos específicos del *M. pneumoniae* en el dominio V del rRNA 23S; lo que hace que el peptidil tRNA se disocie del ribosoma e impida la síntesis de proteínas. Cuando se produce una mutación puntual en el bucle de la peptidil transferasa del rRNA 23S del *M. pneumoniae* se produce la resistencia a macrólidos.

Es importante el estado inmunitario del huésped, porque va a repercutir en la respuesta inmune contra el *M. pneumoniae* y por tanto en la gravedad de la infección aguda o en las manifestaciones extra-respiratorias.

EPIDEMIOLOGÍA

Muchos de los casos de enfermedad por *M. pneumoniae* presentan síntomas similares a los de otras infecciones respiratorias agudas y es frecuente que queden sin diagnóstico etiológico. Las infecciones producidas por *M. pneumoniae* no se recogen en el sistema nacional de vigilancia, por ello, aunque son infecciones comunes, no se dispone de información epidemiológica para toda España. Se estima que anualmente ocurren unos 2 millones de casos de neumonía por *M. pneumoniae* en Estados Unidos, lo que resulta unas 100.000 hospitalizaciones al año, aunque la cifra puede ser mayor ya que muchas de ellas no se informan [6].

Las infecciones son tanto endémicas como epidémicas en todo el mundo. Generalmente las ondas epidemias ocurren cada 4-7 años [7]. Se supone que estas fluctuaciones están relacionadas con cambios antigénicos en las cepas de Mycoplasma, disminución de la inmunidad colectiva en las poblaciones o la combinación de ambos [8,9]. Durante los brotes epidémicos, *M. pneumoniae* puede ser responsable de hasta el 25% de los casos de neumonía asociada a la comunidad [10], esta proporción cae al 1-8% en periodos interepidémicos [11].

Las epidemias ocurren más frecuentemente en entornos cerrados o semicerrados de la comunidad, como colegios, guarderías, hospitales, cuarteles militares, comunidades religiosas o dentro del núcleo familiar [12,13].

Las infecciones por *M. pneumoniae* pueden afectar tanto a niños como a adultos. La mayor parte de las infecciones son autolimitadas, sobre todo en adultos. Son excepcionales en niños menores de un año y son más frecuentes entre 5 y 15 años de edad [14]. Pueden ocurrir en cualquier época del año sin variaciones estacionales importantes.

Se transmite de persona a persona por gotitas respiratorias infectadas en el contacto cercano. El periodo de incubación es de 2 a 3 semanas.

Una mutación en el asa de peptidil transferasa de 23S rRNA generó resistencia a los macrólidos, y el mecanismo clave para cambiar la susceptibilidad a los macrólidos es una mutación puntual. Antes del año 2000, solo unos pocos casos de *M. pneumoniae* resistentes a macrólidos se habían informado en varios países. Sin embargo, la prevalencia reciente de resistencia a los macrólidos en China y Japón se estimó en 79,7% y 53,7%, respectivamente [3]. La resistencia de *M. pneumoniae* a los macrólidos ha aumentado la preocupación con respecto al fracaso del tratamiento, cambio de antibiótico y duración de la enfermedad. A pesar de los avances en la detección molecular tales pruebas rara vez se llevan a cabo en atención primaria [3]. Esto es debido a que *M pneumoniae* tiene requerimientos especiales para el crecimiento, no crece en una palca de cultivo convencional como las utilizadas para el resto de bacterias y la detección de resistencias requiere una técnica de secuenciación.

CLÍNICA

Muy frecuentemente, la infección por *M. pneumoniae* es asintomática, sobre todo en adultos. Cuando la infección se hace clínicamente manifiesta, es habitual la afectación del tracto respiratorio superior, y es difícil distinguirla de otras infecciones respiratorias causadas por virus u otras bacterias atípicas [2,14].

Tabla 1 **Complicaciones extra-respiratorias más importantes de la infección por *M. pneumoniae*. [15, 17, 51].**

Dermatológicas	Síndrome de Stevens- Johnson (agente infeccioso más frecuente asociado a este síndrome), exantema, eritema multiforme, urticaria.
Neurológicas	Meningoencefalitis, encefalitis, meningitis, síndrome de Guillain Barré, neuritis óptica
Hematológicas	Anemia hemolítica, anemia autoinmune, trombocitopenia, purpura de Schonlein-Henoch,
Cardiacas	Miocarditis, pericarditis, endocarditis
Musculoesqueléticas	Mialgias, artritis, rabdomiólisis.
Digestivas	Gastritis, pancreatitis, hepatitis.
Otras	Glomerulonefritis, Enfermedad de Kawasaki

El síndrome más típico, especialmente en niños, es la traqueobronquitis acompañada de una amplia variedad de manifestaciones respiratorias superiores, como faringitis o rinitis. También puede ocasionar manifestaciones en áreas próximas a las vías respiratorias como conjuntivitis o miringitis [15].

La manifestación más frecuente del tracto respiratorio inferior es la neumonía, incluida dentro de las llamadas "neumonías atípicas", que se desarrolla lentamente y puede durar semanas o meses. Los síntomas más frecuentes son escalofríos, fiebre, tos, cefaleas, mialgias, artralgias y malestar general. Destaca una tos persistente que a veces produce dolor torácico. En la auscultación puede detectarse crepitantes dispersos y sibilancias. El derrame pleural es escaso, ocurre en 15-20% de los pacientes con neumonía y el empiema es raro [2].

La mayoría de los casos de neumonía, son leves y limitados, aunque excepcionalmente se han producido casos fulminantes [16].

M. pneumoniae puede producir además manifestaciones extra-respiratorias, que pueden aparecer antes, durante o después de las manifestaciones pulmonares, pero también en ausencia de estas. Estas manifestaciones pueden aparecer hasta en el 25% de los infectados [17], y se producen fundamentalmente por tres mecanismos patogénicos: por acción de la propia bacteria junto a las citoquinas inflamatorias, por un mecanismo de inmunidad e inmunocomplejos o por vasculitis [18,19]. Las patologías extra-respiratorias más frecuentes quedan reflejadas en la tabla 1.

Una de las manifestaciones más importantes, aunque no frecuentes, son las neurológicas incluyendo las encefalitis que se producen sobre todo en niños [20]. De las manifestaciones dermatológicas el síndrome de Stevens-Johnson es la más grave, y las urticarias, y el eritema multiforme que son más frecuentes, probablemente mediadas por inmunocomplejos [21]. Las complicaciones cardiacas son poco frecuentes, tienen pronósticos variables y a menudo se presentan sin evidencia respiratoria [17].

La coinfección de *M. pneumoniae* con otros virus o bacterias es posible y según diferentes estudios puede llegar hasta en un 20%-50% de los casos [20,21].

Se ha escrito mucho de la relación de infección de *M. pneumoniae* con el asma, vinculándose con nueva aparición, exacerbaciones del asma, empeoramiento crónico y la disminución a largo plazo de la función pulmonar [13,22]. Algunos estudios han encontrado que el 46% de los niños con asma aguda tienen infección por *M. pneumoniae* con una estrecha relación entre la exacerbación aguda grave del asma y la infección [23,24]. Un meta-análisis realizado por Liu X et al en el 2021, concluyó que había una asociación estadísticamente significativa entre la infección por *M. pneumoniae* y un mayor riesgo de cualquier tipo de asma infantil. Además, los niños que presentaban un episodio agudo de asma, tenían una seropositividad de anticuerpos IgM frente a *M. pneumoniae* significativamente mayor que los niños que en ese momento presentaban asma estable [25].

El riesgo de hospitalización por infección por *M. pneumoniae* se relaciona con inmunodepresión, comorbilidades y tratamiento no efectivo [26]. En un estudio de los casos confirmados con infección por *M. pneumoniae,* realizado entre 2014 y 2018 en el Servicio Navarro de Salud, se llegó a la conclusión que la neumonía bilateral, las crisis asmáticas y los síntomas extra-respiratorios se asociaron a mayor riesgo de hospitalización [27].

DIAGNÓSTICO

Para realizar el diagnóstico de la infección por *M. pneumoniae* los Servicios de Microbiología Clínica, disponen fundamentalmente de 3 tipos de pruebas: el cultivo, la serología y los métodos de amplificación de ácidos nucleicos. El microscopio óptico no puede detectarlo y tampoco produce turbidez visible en medios de cultivo líquido convencionales. Para obtener una confirmación visual del crecimiento, los cultivos requieren medios especializados de enriquecimiento como son el medio Hayflick modificado o el SP4.

M. pneumoniae es cultivable en medios acelulares, pero presenta exigencias nutricionales complejas lo que hace que sea bastante delicado de realizar. Las muestras aptas para el cultivo incluyen: exudado faríngeo, esputo, aspirado nasal o traqueal, lavado bronquioalveolar o liquido pleural [27]. Las exigencias nutricionales y el tiempo necesario para su cultivo, 2

a 3 semanas, hacen que sea poco útil para un diagnóstico rápido. En la actualidad se utiliza para confirmación de aislamiento, caracterización biológica y fundamentalmente para estudio de sensibilidad antibiótica con una especificidad del 100% si el resultado es positivo y detección de posibles resistencias [12].

En ausencia de cultivo, la serología pareada en fase aguda y en fase de convalecencia, de anticuerpos IgM e IgG contra *M. pneumoniae* ha sido el método más utilizado. El problema de esta técnica es que requiere que pasen 4 - 8 semanas para tomar la muestra serológica en la fase de convalecencia, lo que restringe su utilidad en un diagnóstico rápido y en la toma de decisiones. Debido a esta limitación, se ha optado por medir los títulos de IgM en la fase aguda, que aparecen a los 7-10 días de la infección. Sin embargo, los resultados de esta prueba no se consideran fiables debido a que los títulos de Ig M pueden permanecer altos durante meses y posiblemente años, a que es posible que no aparezcan en niños muy pequeños, o durante la reinfección, y a que el valor predictivo positivo de esta prueba puede ser tan solo del 15 % [14]. Los títulos de Ig G son detectables aproximadamente a la quinta semana y puede persistir años después de la infección aguda [28]. Como métodos serológicos se puede utilizar la fijación de complemento, inmunofluorescencia indirecta (IFI), enzimoinmunoanálisis (EIA), microaglutinación de partículas (MAP) y el más utilizado es el inmunoensayo enzimático (ELISA).

Las técnicas de amplificación de ácidos nucleicos, se han convertido gradualmente en un método importante para el diagnóstico temprano y rápido de la infección por *M. pneumoniae,* por su ayuda a instaurar una terapia antibiótica temprana y adecuada. La técnica más utilizada en la actualidad para el diagnóstico es la reacción en cadena de la polimerasa (PCR) en tiempo real. Debido a las ventajas de tiempos de respuesta cortos, alta sensibilidad y especificidad, y no afectarse por la respuesta inmunológica, la PCR se ha convertido en opción preferida para el diagnóstico temprano de *M. pneumoniae* en el medio asistencial [28,29]. Sin embargo, tiene algunas limitaciones, la necesidad de muestras de alta calidad, y la posibilidad de que los inhibidores de la PCR conduzcan a resultado falsos negativos [30].

La detección de *M. pneumoniae* con PCR a tiempo real en muestras respiratorias ha mostrado una sensibilidad del 60% y una especificidad del 96,7% en comparación con la serología [13]. La sensibilidad de las técnicas de amplificación de ácidos nucleicos y la rapidez de respuesta, hacen que se considere "el nuevo estándar de oro" en el diagnóstico de este microorganismo. Muchos autores consideran que la combinación de la PCR y la serología aportan el diagnóstico más correcto y fiable de la infección por *M. pneumoniae* [2,12,17].

TRATAMIENTO

La resolución de infecciones por *M. pneumoniae* sin tratamiento en 7-10 días no es infrecuente [15,17]. Sin embargo, la mayoría de las veces es necesario el tratamiento antibiótico para mejorar los síntomas clínicos, reducir la duración de la enfermedad y para curar las manifestaciones extra-respiratorias [29]. *M. pneumoniae* al carecer de pared celular es resistente a los antibióticos que actúan en ella, como los betalactámicos o glicopéptidos, pero en general es sensible a macrólidos, cetólidos, tetraciclinas y fluoroquinolonas [31,32].

Los antibióticos más utilizados para el tratamiento en las neumonías por este microorganismo, sobre todo en niños, son los macrólidos que tienen acción antiinflamatoria además de antibiótica, lo que contribuye a la mejoría del paciente [30]. Dentro de los macrólidos, la azitromicina, roxitromicina o claritromicina se prefieren a la eritromicina por su mejor tolerancia, su mejor administración y menor duración de tratamiento. Según la Guía Terapéutica Antimicrobiana del Sistema Nacional de Salud (PRAN), en la infancia el tratamiento más utilizado para la neumonía atípica de elección es la azitromicina oral a dosis de 10 mg/kg/día, una dosis al día el primer día (dosis máxima 500 mg) seguida de 5 mg/kg/día (dosis máxima 250 mg/día) los días 2º a 5º. Como alternativa se utiliza la claritromicina oral: 15 mg/kg/ día en dos dosis (máximo 1 gramo /día) durante 7 días.

Rodrigo Gonzalo de Liria et al, defienden que tetraciclinas y fluoroquinolonas se pueden administrar a partir de los 8 años, aunque también pueden ser utilizadas en niños menores con infecciones neurológicas, en las que se recomienda antibióticos que penetren el sistema nervioso central (doxiciclina junto a corticoides a dosis altas). A veces los macrólidos son útiles en estas patologías neurológicas que pueden ser debidas a la respuesta inmunitarias del huésped más que a un efecto directo del *M. pneumoniae* [16].

Ante la sospecha de neumonía adquirida en la comunidad el tratamiento antibiótico ha demostrado disminuir la morbimortalidad del paciente [31,32]. En atención primaria, el diagnóstico de la mayoría de las neumonías en adultos se basa en criterios clínicos y radiológicos, y con frecuencia no se realizan estudios microbiológicos. En estos casos el tratamiento es generalmente empírico y se establece en función de la gravedad del proceso y el perfil de paciente, asumiendo la incertidumbre diagnostica. Solo se llega a un diagnóstico etiológico en el 20-30% de los casos (Guía Terapéutica Antimicrobiana del Sistema Nacional de Salud: https://resistenciaantibioticos.es). En las neumonías *por M. pneumoniae* como en el resto de las neumonías atípicas, el tratamiento de elección se realiza con azitromicina oral 500 mg cada 24 horas durante 3 días o levofloxacino oral 500 mg cada 24 horas durante 5 días.

RESISTENCIA A MACRÓLIDOS

Como consecuencia del uso generalizado de macrólidos las resistencias del *M. pneumoniae* a estos antibióticos están aumentando en todo el mundo de forma preocupante**.** Las tasas de resistencias han aumentado en China del 40% en 2008 a más del 79% en la siguiente década [31]. En Europa las tasas de resistencias varían según los países, desde un 0,2% en Suecia [34] a un 26% en Italia [32]. Las primeras cepas de *M. pneumoniae* resistentes a los macrólidos se detectaron en Asia en

Tabla 2 **Frecuencia de resistencias a macrólidos en infecciones por *M. pneumoniae* en varios países europeos y en diferentes estudios.**

País y autor	% de resistencias
Alemania Dumke (2013) [42] Dumke (2019) [43]	1.2% 3%-3,6%
Escocia Chalker (2012) [44] Ferguson (2013) [45]	0% 19%
España Rivaya (2020) [46]	8%
Dinamarca Uldum (2010) [47]	1%-3%
Finlandia Kurkela (2019) [48]	9,5%
Francia Pereyre (2013) [50] Pereyre (2016) [32]	3.45%-8%
Inglaterra Brown (2015) [51]	9,3%
Italia Chironna (2011) [52] Loconsole (2019) [37]	26%
Suiza Meyer (2014) [34]	2%
Suecia Gullsby (2019) [53]	0,2%

2001 y se relacionaron con el amplio uso de estos antibióticos [35] y desde entonces han aumentado rápidamente. Los fenotipos de resistencia a macrólidos, que se definen por polimorfismos de un solo nucleótido en el dominio V del gen 23rRNA, son más comunes en los niños que en adultos [36,37,38]. Las manifestaciones clínicas de la infección por cepas resistentes, son por lo general similares a las que son sensibles a macrólidos, pero provocan una mayor duración de la fiebre, tos, estancia hospitalaria y administración de antibióticos [39]. La aparición de cepas de *M. pneumoniae* resistentes a macrólidos es un problema de Salud Pública mundial. Hay estudios que encuentran una tasa de resistencia entre el 80%y el 90% en China y Japón [31,40]. En comparación con Asia, la proporción de cepas de resistencias a macrólidos en Europa es bastante baja, pero los estudios de resistencia son escasos. La mayoría de estudios publicados en Europa se deben a diferentes brotes epidémicos de *M. pneumoniae*, ya que la mayoría de los países europeos no tienen un sistema de vigilancia de infecciones y de resistencias a macrólidos de este microorganismo, lo que subestima la verdadera prevalencia. En un reciente estudio realizado por Wang et al sobre la prevalencia mundial de resistencia a macrólidos en *M. pneumoniae* detectó que la resistencia media en Europa es en torno al 3%, obteniendo datos de prevalencia diferentes a lo largo del tiempo. En Europa antes del año 2008 había una prevalencia media de 0.8%, y en el año 2018-2020 la prevalencia media es del 10% [41]. Según la revisión publicada en 2021 por Loncosole et al, la prevalencia más alta en Europa se registra en Italia y Escocia sobre todo a consecuencia de las epidemias que tuvieron en el periodo 2010-2011 [37]. En la tabla 2 se compara las resistencias a macrólidos del *M. pneumoniae* en países europeos a lo largo de los diferentes años de estudio. En Alemania en el año 2003-2008 se encontró una resistencia a macrólidos de 1.2%, aumentando en posteriores estudios a 3,6% [42,43]. En Gales el año 2010 presentaba un 0% de resistencias aumentando en el año 2013 a un 19% [44,45]. En España hay muy pocos estudios que informen de la prevalencia de resistencia a macrólidos. El primer caso publicado se detectó en 2014 en una estudiante de China, que volvió durante 13 días a su país de origen y tuvo una neumonía [46]. Un estudio realizado en el servicio de urgencias del Hospital Universitario Germans Trias i Pujol de Badalona con muestras recogidas entre el 2013 y 2017, encontró un 8% de resistencias [47]. En países como Finlandia el porcentaje de resistencias oscila en un 9,5% [48]. La prevalencia notificada de resistencias a macrólidos en *M. pneumoniae* en Francia en el período endémico 2007-2010 fue del 3,4% Sin embargo en el año 2011 hubo un brote en la zona de Burdeos con un 8,3% de resistencias [36,51]. En Italia, la primera identificación de infección por *M. pneumoniae* resistente a macrólidos fue en el año 2010 durante un brote epidémico, estimándose que la prevalencia era del 26% [37,52]. En otros países europeos como Suiza, se encontró una prevalencia de 2% en el periodo 2011 al 2013 y en Suecia según un estudio realizado durante los años 1996-2017 se encontró cepas de resistencia a macrólidos en un 0,2% [34,53]. En Eslovenia en un estudio retrospectivo durante los años 2006-2014 se detectó en las infecciones por *M. pneumoniae* una resistencia de tan solo un 1% [54]. En otros países no europeos también se han estudiado las tasas de resistencia a macrólidos como las encontradas en Estados Unidos con una tasa de 3,5%- 13% y en Israel en torno al 30% [55,56]. Respecto al tratamiento en niños con infecciones por *M. pneumoniae* resistente a macrólidos, el uso de tetraciclina y fluoroquinolonas es generalmente tolerable, pero dado que pueden producir efectos secundarios en la infancia, se necesita vigilar y considerar los beneficios y riesgos individualmente para decidir su uso [57,58]. En países con alta proporción de cepas resistentes como Japón, se ha probado el tratamiento con tosufloxacino o minociclina como medicamentos de segunda línea para niños con neumonía por *M. pneumoniae* que responden mal a macrólidos obteniéndose buenos resultados [59,60].

CONCLUSIONES

Las infecciones por *M. pneumoniae* son frecuentes, aunque se desconoce su verdadera incidencia. Generalmente son infecciones benignas, pero pueden producir patologías respira-

torias y extra-respiratorias graves.

Debido a su crecimiento lento en cultivo y a la falta de disponibilidad de pruebas de susceptibilidad fenotípica, en niños el tratamiento antimicrobiano se inicia con macrólidos de forma empírica, obviando la posibilidad de resistencia. La PCR en muestras respiratorias puede ser de gran utilidad para mejorar el diagnóstico etiológico de los casos e instaurar el tratamiento dirigido. Las cepas resistentes se están extendiendo en todo el mundo convirtiéndose en un problema potencial de salud pública. Es necesario realizar más estudios para conocer la incidencia de las infecciones por *M. pneumoniae* y conocer la incidencia de las resistencias a macrólidos en nuestro medio y en los diferentes países.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

BIBLIOGRAFÍA

1. Chanock RM. *Mycoplasma pneumoniae*: proposed nomenclature for atypical pneumonia organism (Eaton agent). Science. 1963;10;140(3567): 662. doi: 10.1126/science.140.3567.662.
2. Quiles Machado JA, Aragón Domínguez V, Monsalvo Hernando M, Gómez Durán M. Neumonías bacterianas no neumocócicas (II). Infecciones respiratorias por *Mycoplasma* y *Chlamydia*. Neumonías víricas [Non-pneumococcal bacterial pneumonias (II). Respiratory infections by *Mycoplasma and Chlamydia*. Viral pneumonias]. Medicine (Madr). 2018;12(54):3186-3197. doi: 10.1016/j.med.2018.04.002.
3. Wang G, Wu P, Tang R, Zhang W. Global prevalence of resistance to macrolides in *Mycoplasma pneumoniae*: a systematic review and meta-analysis. J Antimicrob Chemother. 2022; 25; 77(9):2353-2363. doi: 10.1093/jac/dkac170.
4. Razin S, Yogev D, Naot Y. Molecular biology and pathogenicity of *mycoplasmas*. Microbiol Mol Biol Rev. 1998; 62(4): 1094-156. doi: 10.1128/MMBR.62.4.1094-1156.
5. Holzman R.S., Simberkoff M.S. *Mycoplasma pneumoniae* y neumonía atípica. In: Mandel G.L., Bennett J.E., Dolin R., editors. *Mandell Douglas* Enfermedades Infecciosas. Principios y práctica. 8ª ed. Elsevier España; Barcelona. 2016: 2298-2305.
6. Quiles Machado JA, Aragón Domínguez V, Monsalvo Hernando M, Gómez Durán M. Neumonías bacterianas no neumocócicas (II). Infecciones respiratorias por *Mycoplasma y Chlamydia*. Neumonías víricas [Non-pneumococcal bacterial pneumonias (II). Respiratory infections by. Viral pneumonias]. Medicine (Madr). 2018; 12 (54):3186-3197. Spanish. doi: 10.1016/j.med.2018.04.002.
7. Waites KB, Ratliff A, Crabb DM, Xiao L, Qin X, Selvarangan R, et al. Macrolide-Resistant *Mycoplasma pneumoniae* in the United States as Determined from a National Surveillance Program. J Clin Microbiol. 2019; 23; 57(11): e00968-19. doi: 10.1128/JCM.00968-19.
8. Zhang XS, Zhao H, Vynnycky E, Chalker V. Positively interacting strains that co-circulate within a network structured population induce cycling epidemics of *Mycoplasma pneumoniae*. Sci Rep. 2019; 24; 9(1):541. doi: 10.1038/s41598-018-36325-z.
9. Dumke R, Catrein I, Herrmann R, Jacobs E. Preference, adaptation and survival of *Mycoplasma pneumoniae* subtypes in an animal model. Int J Med Microbiol. 2004; 294(2-3):149-55. doi: 10.1016/j.ijmm.2004.06.020.
10. Kenri T, Okazaki N, Yamazaki T, Narita M, Izumikawa K, Matsuoka M, et al. Genotyping analysis of *Mycoplasma pneumoniae* clinical strains in Japan between 1995 and 2005: type shift phenomenon of *M. pneumoniae* clinical strains. J Med Microbiol. 2008; 57(Pt 4):469-475. doi: 10.1099/jmm.0.47634-0.
11. Atkinson TP, Balish MF, Waites KB. Epidemiology, clinical manifestations, pathogenesis and laboratory detection of *Mycoplasma pneumoniae* infections. FEMS Microbiol Rev.2008; 32(6): 956-73. doi:10.1111/j.1574-66976.2008.00129.x.
12. von Baum H, Welte T, Marre R, Suttorp N, Lück C, Ewig S. Mycoplasma pneumoniae pneumonia revisited within the German Competence Network for Community-acquired pneumonia (CAPNETZ). BMC Infect Dis. 2009 13; 9: 62. doi: 10.1186/1471-2334-9-62
13. Kumar S. *Mycoplasma pneumoniae*: A significant but underrated pathogen in paediatric community-acquired lower respiratory tract infections. Indian J Med Res. 2018; 147(1): 23-31. doi: 10.4103/ijmr.IJMR_1582.
14. Atkinson TP, Waites KB. *Mycoplasma pneumoniae* Infections in Childhood. Pediatr Infect Dis J. 2014; 33(1): 92-4. doi: 10.1097/INF.0000000000000171.
15. Bajantri B, Venkatram S, Diaz-Fuentes G. *Mycoplasma pneumoniae*: A Potentially Severe Infection. J Clin Med Res. 2018; 10(7):535-544. doi: 10.14740/jocmr3421w.
16. Rodrigo Gonzalo de Liria C, Méndez Hernández M. Infecciones causadas por *Mycoplasma pneumoniae*. Anales de Pediatria Continuada.; 2013; 11:23-29.
17. Sharma L, Losier A, Tolbert T, Dela Cruz CS, Marion CR. Atypical Pneumonia: Updates on *Legionella, Chlamydophila*, and *Mycoplasma Pneumonia*. Clin Chest Med. 2017;38(1):45-58. doi: 10.1016/j.ccm.2016.11.011.
18. Merida-Vieyra J, Aquino-Andrade A, Ribas-Aparicio RM, De Colsa-Ranero A. Changing the paradigms of *M. pneumoniae* infection in pediatrics. Acta Pediatr Mex. 2017; 38(6):412-426
19. Narita M. Classification of Extrapulmonary Manifestations Due to *Mycoplasma pneumoniae* Infection on the Basis of Possible Pathogenesis. Front Microbiol. 2016; 28; 7:23. doi: 10.3389/fmicb.2016.00023.
20. Narita M. Pathogenesis of neurologic manifestations of *Mycoplasma pneumonia* infection. Pediatr Neurol. 2009; 41(3): 159-66. doi: 10.1016/j.pediatrneurol.2009.04.012.
21. Diaz MH, Cross KE, Benitez AJ, Hicks LA, Kutty P, Bramley AM, et al. Identification of Bacterial and Viral Codetections With *Mycoplasma pneumoniae* Using the TaqMan Array Card in Patients Hospi-

talized With Community-Acquired Pneumonia. Open Forum Infect Dis. 2016; 30; 3(2) : ofw071.doi: 10.1093/ofid/ofw071.

22. Chiu CY, Chen CJ, Wong KS, Tsai MH, Chiu CH, Huang YC. Impact of bacterial and viral coinfection on *Mycoplasma pneumonia* in childhood community acquired pneumonia. J Microbiol Immunol Infect.2015;48(1):51-6. doi: 10.1016/j.jmii.2013.06.006.
23. Wood PR, Hill VL, Burks ML, Peters JI, Singh H, Kannan TR, et al. *Mycoplasma pneumoniae* in children with acute and refractory asthma. Ann Allergy Asthma Immunol.2013; 110(5):328-334.e1. doi: 10.1016/j.anai.2013.01.022.
24. Kassisse E, García H, Prada L, Salazar I, Kassisse J. Prevalence of *Mycoplasma pneumoniae* infection in pediatric patients with acute asthma exacerbation. Arch. Argent.Pediatr.2018;1:116(3):179185. English,Spanish.doi:10.5546/aap.2018.eng.179.
25. Liu X, Wang Y, Chen C, Liu K. *Mycoplasma pneumoniae* infection and risk of childhood asthma: A systematic review and meta-analysis. Microb Pathog. 2021; 155: 104893. doi: 10.1016/j.micpath.2021.104893.
26. Vervloet LA, Vervloet VE, Tironi Junior M, Ribeiro JD. *Mycoplasma pneumonia* related community-acquired pneumonia and parapneumonic pleural effusion in children and adolescents. J. Bras Pneumol. 2012; 38(2): 226-36. English, Portuguese. doi: 10.1590/s1806-37132012000200013.
27. Álvaro Varela AI, Aguinaga Pérez A, Navascués Ortega A, Castilla J, Ezpeleta Baquedano C. Clinical characteristics of patients with *Mycoplasma pneumoniae* infection. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40(8):449-452. doi: 10.1016/j.eimce.2022.08.002.
28. Copete AR, Vera C, Herrera M, Aguilar YA, Rueda ZV, Vélez LA. *Mycoplasma pneumoniae* in Children With and Without Community-acquired Pneumonia. What do PCR and Serology Say? Pediatr Infect Dis J. 2020;39(7): e104-e108. doi: 10.1097/INF.0000000000002636.
29. Waites KB, Atkinson TP. The role of *Mycoplasma* in upper respiratory infections. Curr Infect Dis Rep. 2009;11(3):198-206. doi: 10.1007/s11908-009-0030-6
30. Zhao F, Guan X, Li J, Liu L, Gong J, He L, et al. Real-Time PCR and Quantitative Culture for *Mycoplasma pneumoniae* Load in Pharyngeal Swabs from Children at Preliminary Diagnosis and Discharge. Biomed Res Int.2020; 3; 2020:9814916. doi: 10.1155/2020/9814916.
31. Tang M, Wang D, Tong X, Wu Y, Zhang J, Zhang L, et al. Comparison of different detection methods for *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia. BMC Pediatr.2021;19;21(1):90.doi: 10.1186/s12887-021-02523-4.
32. Pereyre S, Goret J, Bébéar C. *Mycoplasma pneumoniae*: Current Knowledge on Macrolide Resistance and Treatment. Front Microbiol. 2016; 22;7: 974. doi: 10.3389/fmicb.2016.00974.
33. Parrott GL, Kinjo T, Fujita J. A Compendium for *Mycoplasma pneumoniae*. Front Microbiol. 2016; 12;7: 513. doi: 10.3389/fmicb.2016.00513.
34. Meyer Sauteur PM, Bleisch B, Voit A, Maurer FP, Relly C, Berger C, et al. Survey of macrolide-resistant *Mycoplasma pneumoniae* in children with community-acquired pneumonia in Switzerland. Swiss Med Wkly. 2014; 25; 144: w14041. doi: 10.4414/smw.2014.14041.
35. Eccles S, Pincus C, Higgins B, Woodhead M. Guideline Development Group. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. BMJ.2014; 3; 349:g6722.doi: 10.1136/bmj.g6722.
36. Xu C, Deng H, Zhang J, Zhu Y, Rong Q, Quan Y, et al. Mutations in domain V of *Mycoplasma pneumoniae* 23S rRNA and clinical characteristics of pediatric *M. pneumoniae* pneumonia in Nanjing, China. J Int Med Res. 2021; 49(6):3000605211016376. doi: 10.1177/03000605211016376.
37. Loconsole D, De Robertis AL, Sallustio A, Centrone F, Morcavallo C, Campanella S, et al. Update on the Epidemiology of Macrolide-Resistant *Mycoplasma pneumoniae* in Europe: A Systematic Review. Infect Dis Rep. 2021; 2; 13(3):811-820. doi: 10.3390/idr13030073.
38. Gullsby K, Olsen B, Bondeson K. Molecular Typing of *Mycoplasma pneumoniae* Strains in Sweden from 1996 to 2017 and the Emergence of a New P1 Cytadhesin Gene, Variant 2e. J Clin Microbiol. 2019; 24; 57(6): e00049-19. doi: 10.1128/JCM.00049-19.
39. Okazaki N, Narita M, Yamada S, Izumikawa K, Umetsu M, Kenri T, et al. Characteristics of macrolide-resistant *Mycoplasma pneumoniae* strains isolated from patients and induced with erythromycin in vitro. Microbiol Immunol. 2001; 45(8):617-20. doi: 10.1111/j.1348-0421.2001.tb01293.x.
40. Oishi T, Takahashi K, Wakabayashi S, Nakamura Y, Ono S, Kono M, et al. Comparing Antimicrobial Susceptibilities among *Mycoplasma pneumoniae* Isolates from Pediatric Patients in Japan between Two Recent Epidemic Periods. Antimicrob Agents Chemother. 2019; 24;63(7): e02517-18. doi: 10.1128/AAC.02517-18.
41. Wang G, Wu P, Tang R, Zhang W. Global prevalence of resistance to macrolides in Mycoplasma pneumoniae: a systematic review and meta-analysis. J Antimicrob Chemother. 2022; 25;77(9):2353-2363. doi: 10.1093/jac/dkac170.
42. Dumke R, Lück C, Jacobs E. Low rate of macrolide resistance in Mycoplasma pneumoniae strains in Germany between 2009 and 2012. Antimicrob Agents Chemother. 2013;57(7):3460. doi: 10.1128/AAC.00706-13.
43. Dumke R, Ziegler T. Long-Term Low Rate of Macrolide-Resistant *Mycoplasma pneumoniae*Strains in Germany. Antimicrob Agents Chemother. 2019; 25;63(5): e00455-19. doi: 10.1128/AAC.00455-19.
44. Chalker V, Stocki T, Litt D, Bermingham A, Watson J, Fleming D, Harrison T. Increased detection of Mycoplasma pneumoniae infection in children in England and Wales, October 2011 to January 2012. Euro Surveill. 2012;9;17(6):20081.
45. Ferguson GD, Gadsby NJ, Henderson SS, Hardie A, Kalima P, Morris AC, et al. Clinical outcomes and macrolide resistance in *Mycoplasma pneumoniae* infection in Scotland, UK. J Med Microbiol. 2013; 62(Pt 12):1876-1882. doi: 10.1099/jmm.0.066191-0.
46. Caballero Jde D, del Campo R, Mafé Mdel C, Gálvez M, Rodríguez-Domínguez M, Cantón R, et al. First report of macrolide resistance in a *Mycoplasma pneumoniae* isolate causing community-acquired pneumonia in Spain. Antimicrob Agents Chemother. 2014; 58(2): 1265-6. doi: 10.1128/AAC.02325-13.
47. Rivaya B, Jordana-Lluch E, Fernández-Rivas G, Molinos S, Campos

R, Méndez-Hernández M, et al. Macrolide resistance and molecular typing of Mycoplasma pneumoniae infections during a 4 year period in Spain. J Antimicrob Chemother. 2020; 1; 75(10):2752-2759. doi: 10.1093/jac/dkaa256.

48. Uldum SA, Bangsborg JM, Gahrn-Hansen B, Ljung R, Mølvadgaard M, Føns Petersen R, Wiid Svarrer C. Epidemic of Mycoplasma pneumoniae infection in Denmark, 2010 and 2011. Euro Surveill. 2012; 2; 17(5): 20073. doi: 10.2807/ese.17.05.20073-en.
49. Kurkela S, Puolakkainen M, Hokynar K, Nieminen T, Saxen H, Mannonen L, et al. *Mycoplasma pneumoniae* outbreak, Southeastern Finland, 2017-2018: molecular epidemiology and laboratory diagnostic lessons. Eur J Clin Microbiol Infect Dis. 2019; 38(10):1867-1871. doi: 10.1007/s10096-019-03619-7.
50. Pereyre S, Touati A, Petitjean-Lecherbonnier J, Charron A, Vabret A, Bébéar C. The increased incidence of Mycoplasma pneumoniae in France in 2011 was polyclonal, mainly involving M. pneumoniae type 1 strains. Clin Microbiol Infect. 2013 Apr;19(4): E212-7. doi: 10.1111/1469-0691.12107.
51. Brown RJ, Macfarlane-Smith L, Phillips S, Chalker VJ. Detection of macrolide resistant Mycoplasma pneumoniae in England, September 2014 to September 2015. Euro Surveill. 2015; 20(48): 30078. doi: 10.2807/1560-7917.ES.2015.20.48.30078
52. Chironna M, Sallustio A, Esposito S, Perulli M, Chinellato I, Di Bari C, et al. Emergence of macrolide-resistant strains during an outbreak of Mycoplasma pneumoniae infections in children. J Antimicrob Chemother. 2011; 66(4):734-7. doi: 10.1093/jac/dkr003.
53. Gullsby K, Olsen B, Bondeson K. Molecular Typing of *Mycoplasma pneumoniae* Strains in Sweden from 1996 to 2017 and the Emergence of a New P1 Cytadhesin Gene, Variant 2e. J Clin Microbiol. 2019; 24;57(6): e00049-19. doi: 10.1128/JCM.00049-19.
54. Kogoj R, Praprotnik M, MrviĆT, Korva M, Keše D. Genetic diversity and macrolide resistance of Mycoplasma pneumoniae isolates from two consecutive epidemics in Slovenia. Eur J Clin Microbiol Infect Dis. 2018 ;37(1):99-107. doi: 10.1007/s10096-017-3106-5.
55. Lanata MM, Wang H, Everhart K, Moore-Clingenpeel M, Ramilo O, Leber A. Macrolide-Resistant *Mycoplasma pneumoniae* Infections in Children, Ohio, USA. Emerg Infect Dis. 2021;27(6):1588-1597. doi: 10.3201/eid2706.203206.
56. Averbuch D, Hidalgo-Grass C, Moses AE, Engelhard D, Nir-Paz R. Macrolide resistance in *Mycoplasma pneumoniae*, Israel, 2010. Emerg Infect Dis. 2011;17(6):1079-82. doi: 10.3201/eid/1706.101558.
57. Wang Y, Xu B, Wu X, Yin Q, Wang Y, Li J, et al. Increased Macrolide Resistance Rate of M3562 *Mycoplasma pneumoniae* Correlated With Macrolide Usage and Genotype Shifting. Front Cell Infect Microbiol. 2021;12;11: 675466. doi: 10.3389/fcimb.2021.675466.
58. Mikasa K, Aoki N, Aoki Y, Abe S, Iwata S, Ouchi K et al. JAID/JSC Guidelines for the Treatment of Respiratory Infectious Diseases: The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy - The JAID/JSC Guide to Clinical Management of Infectious Disease/Guideline-preparing Committee Respiratory Infectious Disease WG. J Infect Chemother. 2016; 22(7 Suppl):S1-S65. doi: 10.1016/j.jiac.2015.12.019.
59. Yuan X, Liu J, Bai C, Niu W, Wang J, Li P, et al. Tigecycline in the treatment of fulminant *Mycoplasma pneumoniae* pneumonia non-responsive to azithromycin and fluoroquinolone: A case report. Medicine (Baltimore). 2020; 10;99(28): e21128. doi: 10.1097/MD.0000000000021128.
60. Mohammad A-RM, El-Baky RMA, Ahmed EF. *Mycoplasma pneumoniae*: Atypical Pathogen in Community Acquired Pneumonia. J Pure Appl Microbiol. 2020;14(4):2265-2276. doi: 10.22207/JPAM.14.4.04

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Monocyte distribution width (MDW) as an infection indicator in severe patients attending in the Emergency Department: a pilot study

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ABSTRACT

Background. The aim of the present study was to evaluate the diagnostic performance of monocyte distribution width (MDW) as a biomarker for sepsis diagnosis in severe patients attended in the Emergency Department for different conditions and not only infections.

Methods. We performed an observational study in a consecutive prospective cohort including severe patients attending the Emergency Department with different conditions. MDW and other biomarkers were determined from samples obtained during the first care of patients. The diagnostic performance of the different biomarkers was determined based on the final diagnosis at patient discharge.

Results. One hundred two patients, with a mean age of 76.7 (SD 16.5) years were included, 53 being (51.9%) male. Among the patients included, 65 (63.7%) had an infectious disease while the remaining had other different conditions. A MDW cut-off of 20.115 provided the best accuracy to identify infected patients, with a sensitivity of 89.2 (95% CI 79.4-94.7), a specificity of 89.2 (95% CI 75.3-95.7), a positive predictive value of 93.5 (95% CI 84.6-97.5), a negative predictive value of 82.5% (95% CI 68.0-91.3), a positive likelihood ratio of 8.25 (3.26-20.91), and a negative likelihood ratio of 0.12 (0.06-0.24). The area under the receiver operating characteristic curve for infection according to MDW was 0.943 (95% CI 0.897-0.989; p<0.001).

Conclusions. A MDW > 20.115 may be associated with infection and could help to distinguish between infected and non-infected patients in severe patients. These results must be confirmed in new studies due to the limited patient sample included.

Keywords: MDW, Sepsis, NEWS, SOFA, Disease Progression, Emergency Department, Intensive Care Unit

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Ancho de distribución de los monocitos como indicador de infección en pacientes graves atendidos en Urgencias: estudio piloto

RESUMEN

Introducción. El objetivo del presente estudio fue evaluar el desempeño diagnóstico del ancho de distribución de monocitos (MDW) como biomarcador para el diagnóstico de sepsis entre pacientes graves atendidos en el servicio de urgencias por diferentes afecciones y no solo por infecciones.

Métodos. Realizamos un estudio observacional en una cohorte prospectiva consecutiva que incluyó pacientes graves desde el punto de vista clínico que acudían a urgencias con diferentes patologías. El MDW y otros biomarcadores se determinaron a partir de muestras obtenidas durante la primera atención de los pacientes. Se estudio la precisión de los diferentes biomarcadores para apoyar el diagnóstico de infección, basándonos en el diagnóstico final al alta del paciente.

Resultados. Se incluyeron 102 pacientes, con una edad media de 76,7 (DE 16,5) años, siendo 53 (51,9%) del sexo masculino. Entre los pacientes incluidos, 65 (63,7%) pacientes tenían una enfermedad infecciosa y el resto otras condiciones diferentes. Un punto de corte MDW de 20,115 proporcionó la mejor precisión para identificar pacientes infectados, con un sensibilidad de 89,2 (IC 95 % 79,4-94,7), una especificidad de 89,2 (IC 95 % 75,3-95,7), un valor predictivo positivo de 93,5 (IC 95 % 84,6-97,5), un valor predictivo negativo de 82,5% (IC 95% 68,0-91,3), un coeficiente de probabilidad positivo de 8,25 (3,26-20,91), y un coeficiente de probabilidad negativo de 0,12 (0,06-0,24). El área bajo la curva característica operativa del receptor para la infección del MDW fue de 0,943 (IC del 95 %: 0,897-0,989; p<0,001).

Conclusiones. Un MDW > 20.115 se asocia a padecer una enfermedad infecciosa en un paciente grave y podría ayudar

a distinguir entre pacientes infectados y no infectados. Estos resultados deben ser confirmados en nuevos estudios debido a la muestra limitada de pacientes incluidos.

Palabras clave: ancho de distribución de monocitos, Sepsis, NEWS, SOFA, progresión de la enfermedad servicio de urgencias, unidad de cuidados intensivos

BACKGROUND

Sepsis is defined as life-threatening organ dysfunction caused by systemic and dysregulated host response to infection [1]. It is one of the leading causes of hospital mortality and has a great impact on the healthcare system. Early diagnosis of sepsis is essential for the initiation of adequate treatment to improve patient outcomes [2-4].

Nevertheless, there is no gold standard diagnostic test for sepsis and identification is based on clinical scores. Moreover, the definition of sepsis has changed over time. Multiple studies and guidelines have been published to correctly identify the presentation of sepsis and septic shock using different scores or biomarkers in infected patients [5-7]. The 3rd International Consensus Conference on the Definitions of Sepsis [8] recommends the use of Quick Sequential Organ Failure Assessment (qSOFA) to identify patients with sepsis in the Emergency Department (ED). The recently published Surviving Sepsis Campaign guidelines recommend against the use of qSOFA alone as a screening tool for sepsis or septic shock compared to the systemic inflammatory response syndrome (SIRS), National Early Warning Score (NEWS) or Modified Early Warning Score (MEWS) [9].

There is increasing evidence that monocytes undergo morphological changes, including an increase in volume, during inflammatory/infectious processes and sepsis [10-13]. Monocyte activation and the morphological changes that occur in early inflammatory response can be detected by measuring the monocyte distribution width (MDW) [1], which is a measure of the dispersion related to the mean monocyte population volume in whole blood. The incorporation of the MDW improves the detection of sepsis compared with the white blood count (WBC) alone at the time of ED admission and complements the use of the SIRS and qSOFA parameters that are currently used for this purpose [14,15]. A MDW value greater than 22.0 U is effective for the detection of sepsis based on either Sepsis-2 or Sepsis-3 criteria during the initial ED visit [16]. Therefore, as suggested by some authors, MDW may represent an early indicator of infection and sepsis [17-21].

Nonetheless, infection must first be suspected and several conditions, including anaphylaxis, gastrointestinal emergency, pulmonary disease, metabolic alterations, toxin ingestion/withdrawal, vasculitis, or spinal injury, can mimic sepsis due to the common pathophysiologic responses that these diseases present [22]. All these conditions can be deadly if not correctly diagnosed and managed appropriately. Indeed, the most common errors with therapeutic repercussion in relation to clinical diagnosis and necropsy studies are bacterial infections and cardiovascular diseases [23,24]. Data suggest that as many as 40,500 adult patients in Intensive Care Units (ICU) in the United States may die annually due to misdiagnosis [**25**]. This problem is becoming more common in the evaluation of the elderly and immunosuppressed population in the ED since they may present with atypical clinical manifestations. Differentiating between sepsis and other types of infection or disease can be difficult in the emergency setting and clinical scores or laboratory abnormalities do not provide a definitive diagnosis. However, a combination of history, physical examination, and adjunctive studies may assist healthcare providers.

The aim of the present study was to evaluate the diagnostic performance of MDW as a biomarker for sepsis diagnosis in severe patients attended in the ED setting for different conditions and not only infections.

METHODS

Study Design and Ethical Approval. This was an observational cohort study including consecutive severe patients attended in the ED from November 2020 to February 2021. The study was performed according to the principles of the Declaration of Helsinki and ethical approval was granted by the local Ethics Committee (xxx number). The study coordinator was responsible for collecting and recording all the clinical data using a standardized case report form for each patient throughout the investigation. Informed consent was not required because residual material was used and no interventions were performed beyond routine good standard clinical practices.

Study setting. The ED and Laboratory participating in the study belong to a university hospital with 800 beds and all the medical specialties available. A mean of 350 patients are attended in the ED every day.

Patient and sample selection. Adult patients ≥18 years of age evaluated in the ED with severe clinical manifestations were consecutively included in the study. Disease severity was defined as a NEWS score >5, an increase of 2 points in the Sequential Organ Failure Assessment (SOFA) score or a lactate value > 4 mmol/L. Obstetric/Gynaecology patients were excluded. This was a pilot study and it was decided to finalize the study after 4 months, independently of the sample collected.

Definition and collection of variables. Demographic variables (age. sex) as well as comorbidities were collected. Final diagnosis at hospital discharge and the source of infection in infected patients was recorded. In addition, haemodynamic data (blood pressure, heart rate, respiratory rate, alteration in consciousness according to the Glasgow score, oxygen saturation) and analytical data available during the ED evaluation were registered. The information was collected anonymously in an electronic data collection registry.

MDW determination. Upon request by the attending ED clinician, a whole-blood sample was collected in a K2-EDTA tube and analysed in a UniCel DxH-900 Hematology Analyzer (Beckman Coulter. Inc. Brea. California) within two hours of ex-

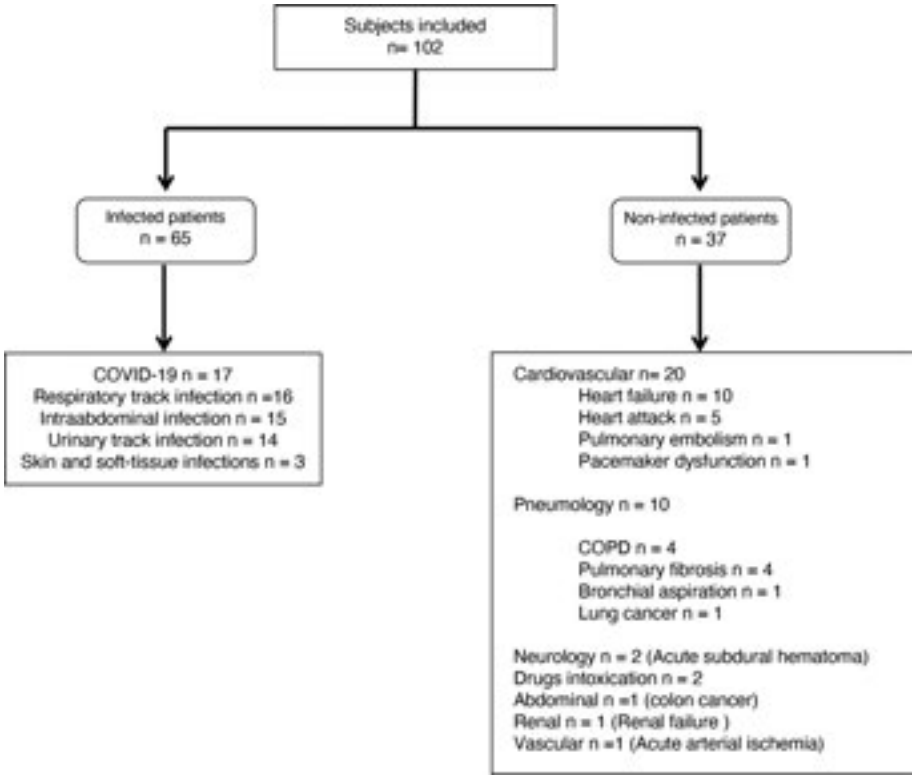


Figure 1 | **Flow diagram of the patients included in the study.**

COVID-19 (Coronavirus disease 2019); COPD: Chronic obstructive pulmonary disease

traction. This equipment uses VCS 360 technology that measures and quantifies the morphological characteristics of each cell using volume, conductivity and multiple light scattering angles, and provides a complete blood count with differential (CBC-Diff). It also measures specific cell volume parameters and the distribution of cell volumes, including MDW, and provides quantitative measurement of the amplitude of monocyte distribution calculated as the standard deviation (SD) of a set of monocyte cell volume values. The investigators were blinded to the MDW values during the collection of patient data and classification and the laboratory investigators were blinded to the patients´ diagnoses. No results of MDW were reported to the attending ED physicians and thus, decision making was not influenced by these results.

Statistical analysis. Categorical variables are expressed as numbers and percentages and the quantitative variables as means and SD [as medians and interquartile ranges (IQR) if the distribution was not normal. Normality was tested using the Kolmogorov-Smirnov test. Categorical variables were compared with the Pearson chi-square or Fisher test and quantitative variables using the Student's-t test (or the Mann-Whitney U test if the distribution was not normal). All patients were classified into 2 groups: infected and non-infected patients. The values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LHR+) and negative likelihood ratio (LHR-) were calculated for the identification of infected patients. A receiver-operator characteristic (ROC) curve was constructed to determine the capacity of MDW to identify infected patients. A p-value of <0.05 was considered statistically significant. The statistical analyses were performed using SPSS for Windows 18.0 (SPSS Inc.. Chicago. IL). The STARD statement for reporting studies of diagnostic accuracy was used in this study [26].

RESULTS

One hundred two patients were included. The mean age was 76.7 (SD 16.5) years and 53 (51.9%) were male. Among the patients included, 65 (63.7%) had an infectious disease based on the final diagnosis at hospital discharge, and the remaining patients had other conditions (Figure 1). In 37 (56.9%) of the 65 infected patients a microorganism was isolated from samples obtained in the ED. Regarding outcomes, 9 (8.8%) patients were admitted to the ICU from the ED and 18 (17.6%) died during hospitalization.

Table 1 shows the characteristics of the sample and the

Table 1 **Characteristics of the patients included in the study based on the diagnosis or not of infection.**

	Infected patients (n=65)	Non-infected (n=37)	p
Demographic data			
Age (years) [mean (SD)]	75.8 (16.7)	78.4 (16.2)	0.415
Male [n(%)]	33 (50.8)	20 (54.1)	0.750
Comorbidity			
Cardiovascular [n(%)]	26 (47.3)	17 (60.7)	0.247
Respiratory [n(%)]	18 (32.7)	7 (25)	0.468
Immunodeficiency [n(%)]	3 (5.5)	0 (0)	0.208
Diabetes [n(%)]	20 (36.4)	10 (35.7)	0.954
Chronic renal failure [n(%)]	13 (23.6)	11 (39.3)	0.137
Chronic Liver disease [n(%)]	6 (10.9)	1 (3.6)	0.255
Cancer	6 (10.9)	4 (14.3)	0.655
Central nervous system	23 (41.8)	10 (35.7)	0.591
Clinical signs			
Temperature [median (IQR)]	36.9 (36.6-37.6)	36.6 (36.2-36.7)	0.05
Heart rate [median (IQR)]	89 (72-102)	84 (69-97)	0.44
Respiratory rate [median (IQR)]	15 (15-15)	15 (15-15)	0.188
Systolic blood pressure [median (IQR)]	121 (110-137)	140 (122-158)	0.011
Diastolic blood pressure [median (IQR)]	66 (53-76)	80 (68-93)	0.014
Oxygen saturation [median (IQR)]	95 (93-98)	98 (68-98.5)	0.639
Laboratory data			
White blood cell count (ml/mm3) [mean (SD)]	11.2 (6-16.8)	9.5 (6.6-12.7)	0.296
Creatinine (mg/dL) [median (IQR)]	1.19 (0.9-1.73)	1.13 (0.85-2.24)	0.806
Bilirubin (mg/dL) [median (IQR)]	0.9 (0.5-1.5)	0.8 (0.6-1.3)	0.952
Biomarkers			
C-reactive protein (mg/L) [median (IQR)]	11.5 (2.8-19.2)	0.94 (0.31-1.98)	<0.001
Procalcitonin (mg/dL) [median (IQR)]	0.28 (0.15-2.57)	0.10 (0.04-0.19)	0.001
Lactate (mg/dL) [median (IQR)]	1.7 (1.25-2.45)	1.3 (0.27-2.72)	0.730
Troponin (mg/dL) [median (IQR)]	0.02 (0.01-0.11)	0.19 (0.04-0.92)	0.009
MDW (U) [median (IQR)]	24.65 (22.06-30.22)	18.41 (16.72-19.50)	<0.001
Severity			
NEWS score [median (IQR)]	4 (3-5)	3 (2-4)	0.032
SOFA score [median (IQR)]	3 (2-3.5)	3 (2-4)	0.158
Outcomes			
ICU admission [n(%)]	6 (9.2)	3 (8.1)	0.848
Mortality [n(%)]	16 (24.6)	2 (5.4)	0.014

IQR: interquartile range; U: units; NEWS: National Early Warning Score; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit

Table 2 Performance of MDW to identify infection between severe patients evaluated in the Emergency Department

	Value	95% CI
Sensitivity	89.2	79.4-94.7
Specificity	89.2	75.3-95.7
Positive predictive value	93.5	84.6-97.5
Negative predictive value	82.5	68.0-91.3
LR (+)	8.25	3.26-20.91
LR (-)	0.12	0.06-0.24

LR (+): positive likelihood ratio; LR (-): negative likelihood ratio.

univariate analysis based on the diagnosis or not of infection. Statistically significant differences were observed in the temperature (higher in infected patients) and blood pressure (lower in infected patients). There were no differences in sex, age, or comorbidity between the two groups. Regarding severity, infected patients had a higher NEWS score, but there were no differences in the SOFA score. Table 1 also shows the biomarker results and the univariate analysis based on the diagnosis or not of infection. Infected patients had higher values of procalcitonin (PCT), C-reactive protein (CRP), and MDW, and lower troponin values. Regarding severity, the NEWS score was higher in infected patients while the SOFA score was similar in both groups.

An MDW cut-off of 20.115 provided the best accuracy to identify infected patients, with a Se of 89.2 (95% CI 79.4-94.7), a Sp of 89.2 (95% CI 75.3-95.7), a PPV of 93.5 (95% CI 84.6-97.5), a NPV of 82.5% (95% CI 68.0-91.3), an LHR+ of 8.25 (3.26-20.91), and an LHR- of 0.12 (0.06-0.24) (Table 2).

On comparing infected with non-infected patients, we observed a tendency of MDW (odds ratio [OR] 1.82 95%CI 0.93-3.58; p=0.08) to be significantly associated with infection (Figure 2). None of the other parameters evaluated (temperature, systolic or diastolic blood pressure, PCT, CRP, or troponin) achieved significance to identify this infected population.

The area under the ROC curve (AUROC) for infection using the MDW was 0.943 (95% CI 0.897-0.989; p<0.001), and 0.847 (95% CI 0.720-0.973; p=0.001) for PCT (Figure 3).

DISCUSSION

The MDW is a measure of monocyte anisocytosis and in this observational study it has shown good accuracy for the identification of infected patients in a cohort of severe patients attended in the ED. The best cut-off was 20.115 with a LHR+ of 8.25, a LHR- of 0.12, and an AUROC for infection of 0.943.

Diagnosis of Infection can be challenging. Multiple studies have described misdiagnosis during the initial approach in severe patients, leading to the initiation of unnecessary or erroneous treatments. Klein Klouwenberg *et al.* [27] reported that among patients admitted to the ICU for sepsis, 13% did not present an infectious disease and in the 30% it was only possible. The study concluded that the diagnosis of sepsis at admission corresponds poorly with the final diagnosis.

In clinical practice decision-making must not only be made based on biomarkers. Nonetheless, biomarkers are helpful tools for clinicians, since the use of only clinical evaluation may not be sufficiently accurate to establish the final diagnosis of the patient, especially in a setting such as the ED in which overcrowding is frequent. Our data show that MDW could be useful in a high-risk population, in which misdiagnosis could lead to erroneous treatment, and therefore, to poor patient outcomes.

The most important feature of a biomarker is its potential to change clinical decision-making. Likelihood ratios may be relevant for evaluating biomarkers and their usefulness for clinicians. An LHR+ between 5 and 10, and a LHR- between 0.1 and 0.2, indicates that the MDW has good performance to induce changes from pre-test probabilities to the final diagnosis, and thus, be clinically relevant [28]. MDW could provide information about the probability that a patient with a positive or negative test actually has or does not have infection.

Several previous studies have described the use of MDW as a screening tool for the early identification of patients at risk of sepsis in the ED [1,29,30], reporting improved detection of sepsis compared with the WBC count, CRP or SIRS, and concluding that MDW had the best discriminatory power for sepsis, based on either Sepsis-2 or Sepsis-3 criteria [14,16,17]. Piva *et al.* [31] showed that MDW values in ICU patients were significantly higher in patients with sepsis or septic shock compared to those within the non-sepsis group. In addition, increase in MDW values was not affected by the aetiology of sepsis, even in patients with COVID-19. A systematic review and meta-analysis including 10 studies including 9,475 individuals, 1,370 of whom had sepsis (742 according to Sepsis-2 and 628 according to Sepsis-3), described a pooled Se and Sp of 0.789 and 0.777 for Sepsis-2 criteria, and 0.838 and 0.704 for Sepsis-3 criteria, being data similar to that obtained in our study. The conclusion of this study was that MDW represents a reliable biomarker for the screening of sepsis [32].

The cut-offs used in these previous studies differed, ranging from 20-27, but this discrepancy can be explained by the different clinical settings in which the studies were performed or the type of study population included. The inclusion of MDW in guidelines defining its exact use and cut-off values as an early indicator of infection and sepsis is necessary since discrepancies have been observed in different studies. Another systematic review concluded that diagnostic thresholds for sepsis should be chosen taking into account the reference standard and tube type used [33]. The implementation of this biomarker in routine practice would require consensus.

PCT is the classical biomarker for the diagnosis of infection in current clinical practice, with several studies reporting the accuracy of PCT in the identification of bacterial infections

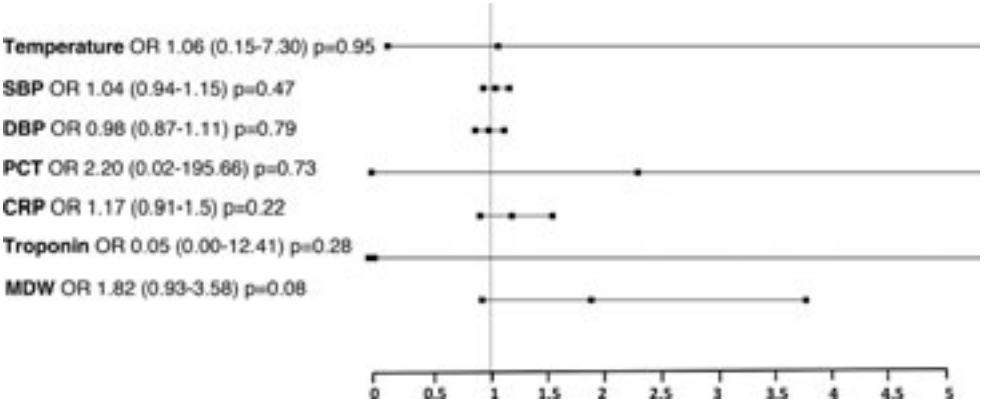
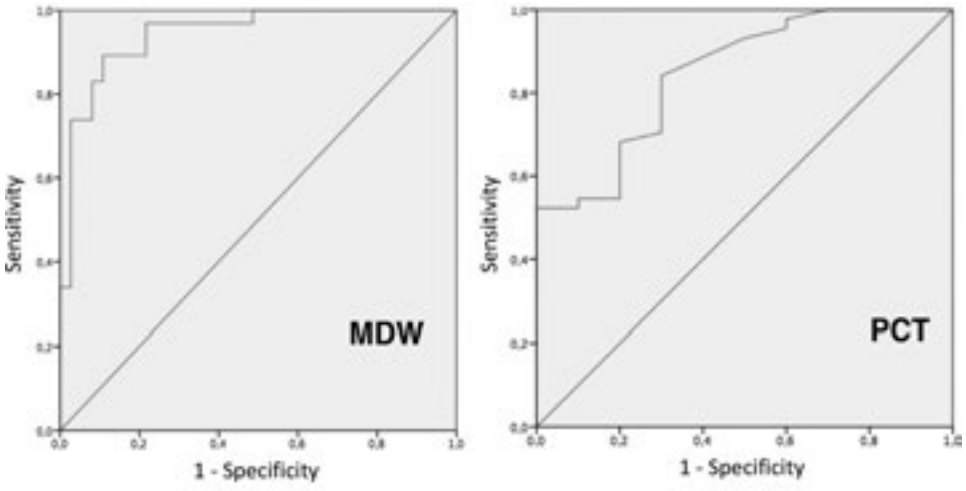


Figure 2 | **Identification of infection between severe patients attended in the Emergency department.**

SBP: systolic blood pressure; DBP: diastolic blood pressure; PCT: procalcitonin; CPR: C-reactive protein



	AUC	95% IC	P value
PCT	0.847	0.720-0.973	0.001
MDW	0.943	0.897-0.989	<0.001

Figure 3 | **ROC curve of MDW and PCT to identify infection between severe patients attended in the Emergency Department.**

and patients with bacteraemia. In our study, the AUROC to identify infected patients was higher for MDW than for PCT, albeit without statistical significance. Moreover, PCT levels provide clinicians with information about the patient´s prognosis or clinical response to antibiotic treatment and can even lead to a reduction in mortality and increase the use of short courses of antibiotics [5,6,34]. Therefore, PCT determination has several advantages compared with MDW, giving physicians additional information apart from the diagnosis. On the other hand, one of the main advantages when comparing MDW with other classical inflammatory markers is that it can be reported automatically. The CBC-Diff is routinely ordered in the ED, and thus, MDW can be determined using routine methods making it an economical, easy-to-use biomarker that can be readily available to clinicians. MDW determination does not require the collection of a different blood sample or any other special request and nor does it involve an extra cost or work. Consequently, the main advantages of MDW are the immediacy of results, accessibility in most centres, and low cost, resulting in high viability for inclusion in clinical practice. Moreover, MDW

values are elevated not only in bacterial infections, but also in virus, even in COVID-19, and fungal infections leading to the identification of infected patients and not only patients with bacterial infection [30]. Previous studies have shown that the MDW index could be a useful tool for early identification of patients at higher risk of unfavourable COVID-19 and for monitoring the progression of viral infection, clinical outcomes, and therapeutic efficacy throughout hospitalization [35].

Our study has some limitations. First, only 102 patients were included, which could influence some results. The OR of MDW for infection was 1.83 (0.93-3.58), which means there is no association between exposure and outcome. Nevertheless, a statistical trend to significance was observed (p=0.008) and the low OR may be a consequence of the limited sample size of our study. Second, this was a unicentric study which precludes the generalization of the results. However, it was performed in a university hospital, the characteristics of which have been previously described and are similar to the majority of European university hospitals. Third, its retrospective nature may limit the applications of some conclusions. Clinical trials are mandatory to change medical approaches, but this was only a pilot study that may be useful to design new studies along the same line and sample calculation.

The results of this pilot study, including severe patients attended in the ED, show that a MDW > 20.115 may be associated with the presence of infectious disease and could help to distinguish between infected and non-infected patients. A discrepancy between MDW levels and clinical approach could lead to clinicians to consider alternative diagnoses and avoid making erroneous initial diagnoses and treatments, which could lead to worse patient outcomes. The strength of this study is that it was performed in severe patients, in whom treatment decisions have a major impact on patient outcomes, including mortality. These results must be confirmed in new studies due to the limited sample of patients included.

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CONFLICT OF INTEREST

The authors declare no have conflict of interest

REFERENCES

1. Agnello L, Bivona G, Vidali M, Scazzone C, Giglio RV, Iacolino G, Iacona A, Mancuso S, Ciaccio AM, Lo Sasso B, Ciaccio M. Monocyte distribution width (MDW) as a screening tool for sepsis in the Emergency Department. Clin Chem Lab Med. 2020;58:1951-1957. doi: 10.1515/cclm-2020-0417.
2. Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Rubio Díaz R, Huarte Sanz I, Navarro Bustos C, et al; INFURG-SEMES Group. Usefulness of the 5MPB-Toledo model to predict bacteremia in patients with community-acquired pneumonia in the Emergency Department. Rev Esp Quimioter. 2021;34(4):376-382. doi: 10.37201/req/043.2021.
3. Pulido Herrero E, Villanueva Etxebarria A, Aramburu Ojembarrena A, Piñera Salmerón P, Quintana López JM, Esteban González C, et al. Influence of the COPD Assessment Test respiratory item score on the decision to hospitalize patients with disease exacerbation in a hospital emergency department. Emergencias. 2022;34:95-102.
4. Gómez-Morán Quintana M, Horrillo García C, Gutiérrez Misis A, Quesada-Cubo V, Torres Poza A, Cintora Sanz A, et al. Factors associated with in-hospital mortality and readmission in a cohort of patients treated with noninvasive ventilation during emergency department or out-of-hospital emergency care: the VentilaMadrid study. Emergencias. 2022;34:7-14.
5. Rubio-Díaz R, Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, et al; on behalf of INFURG-SEMES. Ability of lactate, procalcitonin, and criteria defining sepsis to predict 30-day mortality, bacteremia, and microbiologically confirmed infection in patients with infection suspicion treated in emergency departments. Emergencias. 2022;34(3):181-189.
6. López-Ayala P, Alcaraz-Serna A, Valls Carbó A, Cuadrado Cenzual MA, Torrejón Martínez MJ, López Picado A, et al. Procalcitonin concentration in the emergency department predicts 30-day mortality in COVID-19 better than the lymphocyte count, the neutrophil-tolymphocyte ratio, or the C-reactive protein level. Emergencias. 2022;34:118-27.
7. Álvarez-Kailis S, Paniagua-Arribas E, Paderne-Díaz B, Gómez-García G, Varillas-Delgado D, Padilla-Berdugo R. Value of soluble urokinase plasminogen activator receptor levels in predicting adverse events at 30 days in hospital emergency departments. Emergencias. 2021;33:477-9.
8. Seymour CW, Liu VX, Iwashyna TJ et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8):762–774. doi: 10.1001/jama.2016.0288
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021:1–67. doi: 10.1007/s00134-021-06506-y.
10. Kim MJ, Cheng G, Agrawal DK. Cl channels are expressed in human normal monocytes: a functional role in migration, adhesion and volume change. Clin Exp Immunol 2004;138:453–9. doi: 10.1111/j.1365-2249.2004.02635.x
11. Goasguen JE, Bennett JM, Bain BJ, Vallespi T, Brunning R, Mufti GJ; International Working Group on Morphology of Myelodysplastic Syndrome. Morphological evaluation of monocytes and their precursors. Haematologica 2009;94:994–7. doi: 10.3324/haematol.2008.005421

12. BomansK,SchenzJ,SztwiertniaI,SchaackD,WeigandMA,Uhle F. Sepsis induces a long-lasting state of trained immunity in bone marrow monocytes. Front Immunol 2018;9:2685. doi: 10.3389/fimmu.2018.02685

13.-Tak T, van Groenendael R, Pickkers P, Koenderman L. Monocyte subsets are differentially lost from the circulation during acute inflammation induced by human experimental endotoxemia. J Innate Immun 2017;9:464–74. doi: 10.1159/000475665

14. Crouser ED, Parrillo JE, Seymour C, Angus DC, Bicking K, Tejidor L, Magari R, Careaga D, Williams J, Closser DR, Samoszuk M, Herren L, Robart E, Chaves F. Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker. Chest. 2017;152:518-526. doi: 10.1016/j.chest.2017.05.039.

15. Crouser ED, Parrillo JE, Martin GS, Huang DT, Hausfater P, Grigorov I, Careaga D, Osborn T, Hasan M, Tejidor L. Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. J Intensive Care. 2020;8:33. doi: 10.1186/s40560-020-00446-3.

16. Crouser ED, Parrillo JE, Seymour CW, Angus DC, Bicking K, Esguerra VG, Peck-Palmer OM, Magari RT, Julian MW, Kleven JM, Raj PJ, Procopio G, Careaga D, Tejidor L. Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients. Crit Care Med. 2019; 47:1018-1025. doi: 10.1097/CCM.0000000000003799.

17. Dilmoula A, Kassengera Z, Turkan H, Dalcomune D, Sukhachev D, Vincent JL, and Pradier O. "Volume, conductivity and scatter properties of leukocytes (VCS technology) in detecting sepsis in critically ill adult patients." Blood (ASH Annual Meeting Abstracts), 2011, vol. 118, abstract 4729.

18. Crouser ED, Parrillo JE, Seymour CW, Angus DC, Bicking K, Esguerra VG, et al. Monocyte distribution width: a novel indicator of Sepsis-2 and Sepsis-3 in high-risk emergency department patients. Crit Care Med 2019;47:1018–25. doi: 10.1097/CCM.0000000000003799

19. Lee AJ, Kim SG. Mean cell volumes of neutrophils and monocytes are promising markers of sepsis in elderly patients. Blood Res 2013;48:193–7. doi: 10.5045/br.2013.48.3.193

20. Mardi D, Fwity B, Lobmann R, Ambrosch A. Mean cell volume of neutrophils and monocytes compared with C-reactive protein, interleukin-6 and white blood cell count for prediction of sepsis and nonsystemic bacterial infections. Int J Lab Hematol 2010;32:410–8. doi: 10.1111/j.1751-553X.2009.01202.x

21. Polilli E, Sozio F, Frattari A, Persichitti L, Sensi M, Posata R. Comparison of Monocyte Distribution Width (MDW) and Procalcitonin for early recognition of sepsis. PLoS One 2020;15: e0227300. doi: 10.1371/journal.pone.0227300

22. Long B, Koyfman A. Clinical Mimics: An Emergency Medicine-Focused Review of Sepsis Mimics. J Emerg Med. 2017;52:34-42. doi: 10.1016/j.jemermed.2016.07.102.

23. Bürgesser MV, Camps D, Calafat P, Diller A. Discrepancias entre diagnósticos clínicos y hallazgos de autopsia [Discrepancies between clinical diagnoses and autopsy findings]. Medicina (B Aires). 2011;71:135-8. Spanish. PMID: 21550929.

24. Magret Iglesias M, Vidaur Tello L, Fernández Olsina S, García Fontgivell JF, Blázquez Vilàs S, Alonso Rubio S, Díaz Santos E, Sirvent Calvera JJ, Rello J. Discrepancias entre el diagnóstico clínico y el anatomopatológico en un Servicio de Cuidados Intensivos Polivalente [Discrepancies between clinical and pathological diagnosis in a polyvalent intensive care service]. Med Intensiva. 2006;30:95-100. Spanish. doi: 10.1016/s0210-5691(06)74481-3.

25. Winters B, Custer J, Galvagno SM Jr, Colantuoni E, Kapoor SG, Lee H, Goode V, Robinson K, Nakhasi A, Pronovost P, Newman-Toker D. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. BMJ Qual Saf. 2012;21:894-902. doi: 10.1136/bmjqs-2012-000803.

26. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al; Standards for Reporting of Diagnostic Accuracy. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ. 2003;326:41-4. doi: 10.1136/bmj.326.7379.41

27. Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015;19:319. doi: 10.1186/s13054-015-1035-1.

28. Yang S, De Angelis D. Maximum likelihood. Methods Mol Biol. 2013;930:581-95. doi: 10.1007/978-1-62703-059-5_24.

29. Woo A, Oh DK, Park CJ, Hong SB. Monocyte distribution width compared with C-reactive protein and procalcitonin for early sepsis detection in the emergency department. PLoS One. 2021;16:e0250101. doi: 10.1371/journal.pone.0250101.

30. Laínez Martínez S, González Del Castillo J. Usefulness of monocyte distribution width (MDW) as a sepsis biomarker. Rev Esp Quimioter. 2022;35 (Suppl 1):2-5. doi: 10.37201/req/s01.01.2022.

31. Piva E, Zuin J, Pelloso M, Tosato F, Fogar P, Plebani M. Monocyte distribution width (MDW) parameter as a sepsis indicator in intensive care units. Clin Chem Lab Med. 2021;59:1307-1314. doi: 10.1515/cclm-2021-0192.

32. Agnello L, Vidali M, Lo Sasso B, Giglio RV, Gambino CM, Scazzone C, Ciaccio AM, Bivona G, Ciaccio M. Monocyte distribution width (MDW) as a screening tool for early detecting sepsis: a systematic review and meta-analysis. Clin Chem Lab Med. 2022;60(5):786-792. doi: 10.1515/cclm-2021-1331.

33. Malinovska A, Hernried B, Lin A, Badaki-Makun O, Fenstermacher K, Ervin AM, Ehrhardt S, Levin S, Hinson JS. Monocyte Distribution Width as a Diagnostic Marker for Infection: A Systematic Review and Meta-Analysis. Chest. 2023:S0012-3692(23)00122-8. doi: 10.1016/j.chest.2022.12.049.

34. De Santos Castro PA, Alonso Avilés R. Sobre la capacidad de lactato, procalcitonina y los criterios definitorios de sepsis para predecir mortalidad a 30 días, bacteriemia o infección confirmada microbiológicamente en los pacientes atendidos por sospecha de infección en urgencias. Emergencias. 2022;34:406-406.

35. Ligi D, Lo Sasso B, Henry BM, Ciaccio M, Lippi G, Plebani M, Mannello F. Deciphering the role of monocyte and monocyte distribution width (MDW) in COVID-19: an updated systematic review and meta-analysis. Clin Chem Lab Med. 2023. doi: 10.1515/cclm-2022-0936.

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Cambios en la resistencia antibiótica en episodios de bacteriospermia sintomática: Evolución en un área de salud del sudeste español

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RESUMEN

Objetivo. La prostatitis crónica bacteriana (PCB) es una entidad de difícil diagnóstico clínico y tratamiento, siendo el estudio microbiológico del semen la principal prueba diagnóstica. Este estudio tuvo como objetivo determinar la etiología y la resistencia antibiótica en pacientes con bacteriospermia sintomática (BPS) en nuestro medio.

Material y métodos. Se ha realizado un estudio descriptivo, transversal y retrospectivo, en un Hospital Regional del sudeste español. Los participantes fueron pacientes asistidos en las consultas del Hospital con clínica compatible con PCB entre 2016 y 2021. Se recogieron y analizaron los resultados del estudio microbiológico de la muestra de semen. Se evaluó la etiología y la tasa de resistencia antibiótica de los episodios de BPS.

Resultados. El principal microorganismo detectado es *Enterococcus faecalis* (34,89%), seguido por *Ureaplasma* spp. (13,74%) y *Escherichia coli* (10,98%). La tasa de resistencia antibiótica de *E. faecalis* a las quinolonas (11%) es inferior a estudios previos, mientras que, para *E. coli* ha sido superior (35%). Destaca la baja tasa de resistencia que muestran *E. faecalis* y *E. coli* a fosfomicina y nitrofurantoína.

Conclusiones. En las BPS las bacterias grampositivas y las atípicas se establecen como los principales agentes causales de esta entidad. Esto obliga a replantear la estrategia terapéutica utilizada, lo cual evitará el aumento en las resistencias antibióticas, las recidivas y la cronicidad de esta patología.

Palabras clave: bacteriospermia sintomática; bacterias grampositivas; bacterias atípicas; resistencia antibiótica; tratamiento.

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Antibiotic resistance changes in episodes of symptomatic bacteriospermia: development in a health area of southeast Spain

ABSTRACT

Background. Chronic bacterial prostatitis (CBP) is an entity of difficult clinical diagnosis and treatment, being the microbiological study of semen the main diagnostic test. This study aimed to determine the etiology and antibiotic resistance in patients with symptomatic bacteriospermia (SBP) in our environment.

Material and methods. A cross-sectional and retrospective descriptive study has been carried out from a Regional Hospital of the Spanish Southeast. The participants were patients assisted in the consultations of the Hospital with clinic compatible with CBP, between 2016 and 2021. The interventions were collection and analysis of the results derived from the microbiological study of the semen sample. The main determinations were the etiology and rate of antibiotic resistance of BPS episodes are analyzed.

Results. The main isolated microorganism is *Enterococcus faecalis* (34.89%), followed by *Ureaplasma* spp. (13.74%) and *Escherichia coli* (10.98%). The rate of antibiotic resistance of *E. faecalis* to quinolones (11%) is lower than previous studies, while for *E. coli* it has been higher (35%). The low rate of resistance shown by *E. faecalis* and *E. coli* to fosfomycin and nitrofurantoin stands out.

Conclusions. In the SBP, gram-positive and atypical bacteria are established as the main causative agents of this entity. This forces us to rethink the therapeutic strategy used, which will avoid the increase in antibiotic resistance, recurrences, and chronicity of this pathology.

Keywords: symptomatic bacteriospermia; gram-positive bacteria; atypical bacteria; antibiotic resistance; treatment.

INTRODUCCIÓN

La prostatitis es el diagnóstico urológico más común en varones menores de 50 años y el tercero en mayores de 50 años. Se estima que alrededor del 25% de los varones van a recibir un diagnóstico de prostatitis a lo largo de su vida, aunque solo un 10% van a tener una etiología infecciosa probada [1]. Los National Institutes of Health (NIH) de los EE. UU. han clasificado la prostatitis en cuatro categorías; entre estas, la categoría II incluye la prostatitis crónica bacteriana (PCB) [2], que se caracteriza por síntomas de prostatitis crónica asociados con una infección bacteriana activa. Para el diagnóstico de PCB es necesario, además, un estudio microbiológico que confirme la etiología infecciosa [3]. La PCB es comúnmente causada por *Escherichia coli* y otras enterobacterias [1]. Sin embargo, actualmente, se reconoce el papel de las bacterias grampositivas y de las bacterias atípicas (*Ureaplasma* spp., *Chlamydia trachomatis, Mycoplasma genitalium*, etc.) como agentes directamente implicados en la etiología de esta entidad [4].

Clásicamente, el tratamiento antibiótico de elección es ciprofloxacino / levofloxacino durante 4-6 semanas. Otros tratamientos de segunda línea son: fosfomicina, eritromicina, trimetoprim-sulfametoxazol y tetraciclina [1]. Al hilo de estas terapias tan prolongadas, que ocurren por las recurrencias frecuentes, se ha demostrado la pérdida de eficacia del tratamiento, así como la aparición de uropatógenos multirresistentes [5,6]. Paralelamente a este hecho, está ocurriendo también una reclasificación de los pacientes, pues gran cantidad de los clasificados inicialmente en la categoría III (sólo con síntomas prostáticos crónicos) realmente tienen una etiología infecciosa, previamente oculta, que es evidenciada con las nuevas estrategias diagnósticas de cultivo y biología molecular [1].

Todo ello hace necesario encontrar una pauta terapéutica que asuma el viraje etiológico actual, conservando los principios de coste-beneficio y adherencia terapéutica, además de limitar el desarrollo de resistencia antibiótica. Nuestro estudio pretende contribuir en el entendimiento y tratamiento de esta entidad al analizar la etiología y evolución de la resistencia antibiótica en pacientes con bacteriospermia sintomática (BPS) en nuestro medio.

MATERIAL Y MÉTODOS

Se realizó un estudio transversal, descriptivo de carácter retrospectivo, en el que se incluyeron todas las muestras de semen, con BPS, recibidas en el Laboratorio de Microbiología del Hospital Universitario Virgen de las Nieves (HUVN) de Granada, entre el 1 de enero de 2016 y 24 de mayo de 2021, sin criterios de exclusión. Se evaluaron los resultados obtenidos tras el procesamiento microbiológico de la muestra del paciente con el diagnóstico clínico de sospecha de PCB, mediante cultivo y PCR, de agentes productores de lesiones no ulcerativas.

Todas las muestras fueron procesadas siguiendo el protocolo de trabajo normalizado del laboratorio de Microbiología Clínica [7]. A dichas muestras se les realizó cultivo habitual de muestra genitales para bacterias y hongos, y PCR multiplex en la plataforma BD-MAX (Becton Dickinson, Sparks, EE. UU.) para la detección de diferentes agentes etiológicos: BD-MAX CT/GC/TV para la detección de *Trichomonas vaginalis*, *C. trachomatis* y *Neisseria gonorrhoeae*, y BIO-GX para detección de *Mycoplasma hominis*, *M. genitalium*, *Ureaplasma urealyticum* y *Ureaplasma parvum*. Estos últimos desde enero de 2017, ya que durante 2016 se empleó el cultivo Mycoplasma IST 2 (bioMérieux, Marcy l'Etoile, Francia) detectándose *M. hominis* y *Ureaplama* spp., y realizando antibiograma, en caso de recuentos superiores a 10^4 UFC por muestra. Para la identificación de los microorganismos crecidos en el cultivo habitual se utilizaron los sistemas MALDI-TOF Biotyper (Bruker Daltonics, Billerica, EE. UU.) o MicroScan (Beckman Coulter, Barcelona, España), empleándose este último, también para los estudios de sensibilidad a los antibióticos. Se recuperó el valor de la CMI para cada antibiótico ensayado. Los aislados se clasificaron en sensibles, intermedios o resistentes a cada antibiótico de acuerdo con las recomendaciones del CLSI hasta 2019, y desde 2020 de acuerdo con las recomendaciones de EUCAST de ese año.

Se recogieron las variables procedencia de la muestra, microorganismo y edad del paciente facilitadas por el Servicio de Microbiología por medio del SIL MODULAB ® (Laboratorios Werfen, Barcelona, España) (sistema utilizado en el Sistema Sanitario Público de Andalucía como soporte de la historia clínica electrónica) para su posterior evaluación. Posteriormente, se eliminaron a todos aquellos episodios que tenían cultivo de orina positivo. Los episodios con cultivo de semen positivo y de orina negativa se incluyeron en el estudio.

Análisis estadístico. Se realizó un análisis estadístico descriptivo, calculando frecuencias absolutas y relativas para las variables cualitativas, medidas de tendencia central y dispersión para las cuantitativas. La normalidad de los datos se contrastó con la prueba de Kolmogorov-Smirnov. Para comparar el porcentaje de resistencia a los diferentes antibióticos según el año, se aplicó la prueba chi-cuadrado de Pearson. En los casos en los que no se cumplieron las condiciones de aplicabilidad de la prueba (no más del 20% de las frecuencias esperadas inferiores a 5), se utilizó la prueba exacta de Fisher. Se consideró significativo un valor $p < 0,05$. Los datos se analizaron con el software R 4.4.1.

Consideraciones éticas. El protocolo del estudio se llevó a cabo con arreglo a la Declaración de Helsinki y las consideraciones éticas de la investigación epidemiológica. Este fue un estudio no intervencionista, con ninguna investigación adicional a los procedimientos rutinarios. El material biológico se utilizó sólo para el diagnóstico estándar de infecciones del tracto genital, siguiendo las prescripciones de los médicos. No se realizó muestreo adicional ni modificación del protocolo diagnóstico de rutina. Se realizaron los análisis de datos utilizando una base de datos completamente anónima, donde los sujetos fueron sustituidos por episodios infecciosos diferentes, ocurridos al menos con 6 semanas de diferencia del anterior,

si es que lo hubo. La entidad que concedió el permiso para acceder y utilizar los datos fue la Unidad de Gestión Clínica de Microbiología Clínica del Hospital Virgen de las Nieves de Granada, España.

RESULTADOS

Los episodios de BPS positiva procedieron, principalmente, de pacientes hospitalizados (234 / 64,28%), fundamentalmente del Servicio de Urología (163 / 44,78%) y, en segundo lugar, del Servicio de Medicina Interna (32 / 8,79%). Los episodios comunitarios (130 / 35,71%) incluyeron procedieron Centros de Salud, consultas externas hospitalarias y Servicio de Urgencias, destacando las consultas externas de Urología (100 /27,47%). La edad media de los pacientes fue de 46,56 años. En la Tabla 1 se reflejan los microorganismos detectados en los episodios, destacando *Enterococcus faecalis* (127 / 34,89%), seguido de *Ureaplasma* spp. (50 / 13,74%): *U. urealyticum* (19 / 38%) y *U. parvum* (20 / 40%); en el resto (11/ 22%) no se especifica la especie. El tercer patógeno en frecuencia fue *E. coli* (43 / 11,81%), siendo 3 (6,97%) episodios por *E. coli* productoras de β-lactamasas de espectro extendido (BLEE). En el resto (39,6%), se observa una extensa variedad de microorganismos que quedan reflejados en la Tabla 1. *Corynebacterium* spp. fue el cuarto grupo de microorganismo más frecuentemente aislada (21 / 5,77%), destacando la especie *C. glucoronolyticum* (19 / 90,78%), con un aumento progresivo con el paso de los años. Por otra parte, se aislaron 15 (4,12%) *Streptococcus agalactie* y 17 (4,67%) *Klebsiella* spp. En relación con este último microorganismo, las especies predominantes fueron *Klebsiella pneumoniae* (70,22%) y *Klebsiella oxytoca* (29,78%).

La distribución etiológica es similar tanto en las muestras hospitalarias como comunitarias. En ambas, el patógeno más frecuente es *E. faecalis*: 75 (32,33%) y 48 (36,92%), respectivamente. En segundo lugar, se encuentra *Ureaplasma* spp.: 30 (12,93%) y 19 (14,62%) y, en tercer lugar, *E. coli*: 28 (12,07%) y 15 (11,54%), respectivamente. Los tres aislados de *E. coli* BLEE procedieron de episodios hospitalarios de Urología.

El estudio de la evolución de las resistencias antibióticas de *E. faecalis* y *E. coli* se reflejan en la Tabla 2. Cuando se analiza si la evolución de la tasa de resistencia de *E. faecalis* y *E. coli* a lo largo de los años posee significación, no se encontró significación estadística en ningún caso. En el caso de *Ureaplasma* spp., solo los episodios del año 2016 fueron estudiados y mostraron sensibilidad a azitromicina, claritromicina, eritromicina, tetraciclina y doxiciclina.

DISCUSIÓN

La PCB es una entidad clínico-patológica mal definida, difícil de diagnosticar y de tratar [8]. Diversos autores han indicado que los uropatógenos implicados principalmente en esta patología son las bacterias gramnegativas, destacando a las enterobacterias, siendo el papel de las grampositivas, atípicas y anaerobias aún discutible [5,9]. Sin embargo, se ha informado un aumento reciente en la prevalencia de microorganismos grampositivos [10]. Este último hecho concuerda con lo obtenido en nuestro estudio, donde *E. faecalis* fue el agente más frecuentemente aislado (34,89%). Además, si tenemos en cuenta el resto de las bacterias grampositivas, éstas constituirían el 41,21% de los aislados en nuestra muestra, frente al 23,62% que suponen las enterobacterias. Por ello, es fundamental conocer la etiología de la PCB y, a partir de ella, plantear un tratamiento óptimo. Por otro lado, una de las aportaciones fundamentales de este trabajo es la consideración de las bacterias atípicas como agentes potencialmente implicados en la PCB. En nuestro estudio, *Ureaplasma* spp., es el segundo grupo que con mayor frecuencia se detecta (13,74%) en BPS, por encima de *E. coli* y otras bacterias gramnegativas. No obstante, esto no es un hallazgo aislado del HUVN, sino que concuerda con lo hallado en diversos estudios. Concretamente, Brunner et al [11] encontraron que en 82 (13,7%) pacientes con síntomas prostáticos crónicos, *Ureaplasma* spp. podría ser la causa; más recientemente, en el estudio de Choi et al [12], *Ureaplasma* spp. fue el patógeno que con más frecuencia se detectó en pacientes con PCB en el contexto de las consultas de atención primaria, y el segundo si nos referimos al ámbito hospitalario. Otra bacteria atípica cuya implicación en la etiología de la PCB ha sido reconocida es *Chlamydia trachomatis* [13,14]. Sin embargo, en nuestro estudio solo se han detectado en 8 (2,20%) episodios. La principal razón de este bajo número es que en la población estudiada la promiscuidad sexual sea menor.

El segundo análisis que se realizó está en relación con la evolución de las resistencias antibióticas en los últimos años, en el cual destacan dos aspectos. En primer lugar, se observa una aparente disminución de la resistencia de *E. faecalis* a levofloxacino y ciprofloxacino, que no fue estadísticamente significativa y, por otra parte, un aparente aumento en el porcentaje de resistencia antibiótica de *E. coli* a ciprofloxacino y levofloxacino, que tampoco es estadísticamente significativo (Tabla 2). En segundo lugar, muy pocos estudios han investigado la evolución de la resistencia antibiótica de los dos principales microorganismos clásicos causantes de la PCB: *E. faecalis* y *E. coli*. Sólo el estudio de Cai et al [10] realiza un análisis similar entre los años 1997-2008, donde no se observaron diferencias significativas en la evolución del porcentaje de resistencia antibiótica de *E. faecalis* y *E. coli* a ciprofloxacino y levofloxacino. Otro aspecto, que merece la pena remarcar, es que el patrón de resistencias de *E. faecalis* en nuestro estudio es similar en ambas quinolonas. Esto no concuerda con lo observado en diversas publicaciones [15,16], donde *E. faecalis* mostró un porcentaje de resistencia superior frente a ciprofloxacino. En el caso de *E. coli*, el porcentaje medio de resistencia (34,97%) que hemos observado en nuestro estudio es superior al obtenido en el estudio de Cai et al [10]. Esta importante tasa de resistencia antibiótica es común a lo hallado en otros estudios [9,16,17] y puede explicarse porque, al emplear este grupo antibiótico como tratamiento, empírico o no, de primera elección en esta entidad, se ha favorecido la proliferación de aislados de *E. coli* resistentes, facilitando esto la falta de respuesta al tratamien-

Tabla 1 **Agentes etiológicos y frecuencia de detección en pacientes con bacteriospermia sintomática procedentes del Hospital Universitario Virgen de las Nieves, Granada.**

Microorganismo N (%)		2016	2017	2018	2019	2020	2021	TOTAL
Enterococcus faecalis		23 (37,10%)	25 (37,31%)	29 (31,18%)	26 (38,24%)	18 (31,58%)	6 (35,29%)	127 (34,89%)
Otros enterococos		0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3,51%)	0 (0%)	2 (0,55%)
Staphylococcus aureus		0 (0%)	1 (1,49%)	1 (1,08%)	1 (1,47%)	0 (0%)	0 (0%)	3 (0,82%)
Staphylococcus saprophyticus		1 (1,61%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,27%)
Streptococcus agalactie		3 (4,84%)	1 (1,49%)	3 (3,23%)	2 (2,94%)	4 (7,02%)	1 (5,88%)	15 (4,12%)
Streptococcus grupo bovis		2 (3,23%)	1 (1,49%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0,82%)
Streptococcus mitis		1 (1,61%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,27%)
Lactobacillus spp.		1 (1,61%)	0 (0%)	0 (0%)	0 (0%)	1 (1,75%)	0 (0%)	2 (0,55%)
Escherichia coli		12 (19,35%)	8 (11,94%)	7 (7,53%)	6 (8,82%)	5 (8,77%)	2 (11,76%)	40 (10,98%)
Escherichia coli productora de BLEEs		0 (0%)	1 (1,49%)	1 (1,08%)	0 (0%)	1 (1,75%)	0 (0%)	3 (0,82%)
Klebsiella spp.		2 (3,23%)	1 (1,49%)	7 (7,53%)	6 (8,82%)	1 (1,75%)	0 (0%)	17 (4,67%)
Morganella morganii		1 (1,61 %)	6 (8,96%)	4 (4,30%)	0 (0%)	0 (0%)	0 (0%)	11 (3,02%)
Proteus spp.		0 (0%)	2 (2,99%)	2 (2,15%)	0 (0%)	2 (3,51%)	0 (0%)	6 (1,65%)
Citrobacter spp.		0 (0 %)	1 (1,49%)	1 (1,08%)	2 (2,94%)	1 (1,75%)	0 (0%)	5 (1,37%)
Serratia spp.		0 (0%)	2 (2,99%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0,55%)
Enterobacter spp.		0 (0%)	0 (0%)	1 (1,08%)	0 (0%)	1 (1,75%)	0 (0%)	2 (0,55%)
Pseudomona aeruginosa		0 (0%)	0 (0%)	1 (1,08%)	0 (0%)	0 (0%)	0 (0%)	1 (0,27%)
Gardnerella vaginalis		1 (1,61%)	0 (0%)	5 (5,38%)	3 (4,41%)	1 (1,75%)	1 (5,88%)	11 (3,02%)
Mycoplasma hominis		1 (1,61 %)	2 (2,99%)	2 (2,15%)	2 (2,94%)	1 (1,75%)	1 (5,88%)	9 (2,47%)
Chlamydia trachomatis		2 (3,23 %)	1 (1,49%)	2 (2,15%)	1 (1,47%)	2 (3,51%)	0 (0%)	8 (2,20%)
Ureaplasma spp.	Global	12 (19,35%)	12 (17,91%)	13 (13,98%)	8 (11,76%)	4 (7,02%)	1 (5,88%)	50 (13,74%)
	U. parvum	0 (0%)	6 (8,96%)	4 (4,30%)	4 (5,88%)	4 (7,02%)	1 (5,88%)	19 (5,22%)
	U. urealyticum	4 (6,45%)	3 (4,48%)	9 (9,68%)	4 (5,88%)	0 (0%)	0 (0%)	20 (5,77%)
	Ureaplasma spp. (sin especificar)	8 (12,90%)	3 (4,48%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (2,75%)
Aerococcus spp.		0 (0%)	0 (0%)	1 (1,08%)	1 (1,47%)	2 (3,51%)	0 (0%)	4 (1,10%)
Capnocytophaga spp.		0 (0%)	1 (1,49 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,27%)
Candida spp.		0 (0%)	2 (2,99%)	2 (2,15%)	1 (1,47%)	0 (0%)	0 (0%)	5 (1,37%)
Facklamia spp.		0 (0%)	0 (0%)	1 (1,08%)	1 (1,47%)	1 (1,75%)	0 (0%)	4 (1,10%)
Actinobaculum spp.		0 (0%)	0 (0%)	1 (1,08%)	1 (1,47%)	1 (1,75%)	0 (0%)	3 (0,82%)
Bifidobacterium spp.		0 (0%)	0 (0%)	0 (0%)	1 (1,47%)	0 (0%)	0 (0%)	1 (0,27%)
Actinomyces spp.		0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1,75%)	1 (5,88%)	2 (0,55%)
Corynebacterium spp.		0 (0%)	0 (0%)	7 (7,53%)	6 (8,82%)	6 (10,53%)	2 (11,76%)	21 (5,77%)
Trichomonas vaginalis		0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1,75%)	1 (5,88%)	2 (0,55%)
TOTAL		62 (100%)	67 (100%)	93 (100%)	68 (100%)	57 (100%)	17 (100%)	364 (100%)

to y la cronicidad sintomática que ya previamente era muy común por diversos motivos: dificultad de penetración prostática de algunos antibióticos, teoría del biofilm microbiano, etc. Pero quizás, lo más importante, es que estos aislados son similares a los procedentes de las infecciones urinarias, ya que a estas se le atribuye el origen de la PCB, en la mayoría de los casos [16]. Por otra parte, también es reseñable el alto porcentaje de resistencia que *E. faecalis* muestra a eritromicina (50%) y tetraciclina. En el caso de tetraciclina, este hallazgo concuerda con la observado en otras publicaciones [1,15]. Sin

Tabla 2 **Evolución anual del porcentaje de resistencia de diversos antibióticos en aislados de *E. faecalis* y *E. coli*.**

	2016	2017	2018	2019	2020	2021	Porcentaje de resistencia medio
E. faecalis (n=127)							
Ciprofloxacino	26,32%	8,33%	13,79%	13,04%	6,25%	0%	11,29%
Levofloxacino	23,81%	8,33%	13,79%	13,04%	6,25%	0%	10,87%
Eritromicina	55%	50%	55,17%	54,17%	43,75%	66,67%	54,13%
Fosfomicina	4,76%	8,33%	0%	0%	12,50%	0%	4,265%
Nitrofurantoína	0%	0%	0%	0%	0%	0%	0%
Tetraciclina	84,21%	100%	89,66%	92, 28%	81, 25%	66, 67%	85,68%
Rifampicina	0%	-	-	-	-	-	0%
Linezolid	0%	0%	6,90%	0%	0%	0%	1,68%
E. coli (n=43)							
Trimetoprim-sulfametoxazol	28,57%	57,14%	37,50%	40%	16,67%	50%	37,14%
Ciprofloxacino	22,22%	14,29%	50%	40%	33,33%	50%	32,43%
Levofloxacino	-	-	-	-	33,33%	50%	35%
Fosfomicina	0%	0%	0%	0%	0%	0%	0%
Nitrofurantoína	0%	0%	0%	0%	0%	0%	0%

embargo, destaca que eritromicina y el resto de los macrólidos son fármacos potencialmente útiles para el tratamiento de infecciones causadas por *Ureaplasma* spp., *C. trachomatis* o *M. hominis* [18]. Otro dato relevante es la ausencia de resistencias antibióticas a fosfomicina y nitrofurantoína, tanto en el caso de *E. faecalis* como *E. coli*. Diversos autores [8, 10] encontraron porcentajes de resistencia superiores, fundamentalmente en el caso de *E. coli* (11% para fosfomicina y en torno al 13-15% para nitrofurantoína). Para *E. faecalis*, las tasas de resistencia a nitrofurantoína y fosfomicina de Cai et al [10] concuerdan con lo hallado en nuestro trabajo. Si bien con fosfomicina no existe una amplia experiencia clínica y nitrofurantoina se ha empleado como terapia de continuación, para erradicar la bacteriuria que frecuentemente se asocia a la BPS [19].

Los resultados anteriores deberían sustentar las terapias empíricas actuales. Clásicamente las fluoroquinolonas, fundamentalmente ciprofloxacino 1000 mg /24h y levofloxacino 500 mg /24h, durante al menos 28 días, han sido el tratamiento de elección de esta entidad [20-22], encontrándose tasas de respuesta clínica y microbiológica del 70-90% al final de la terapia [22]. En el segundo escalón de tratamiento se encuentran: trimetoprim-sulfametoxazol, tetraciclinas, fosfomicina, macrólidos y nitrofurantoína [23]. Magri et al [24] obtuvieron con la combinación de azitromicina y ciprofloxacino unas tasas de erradicación microbiológica empírica del 75,5% para bacterias típicas y del 82,3% para bacterias atípicas, siendo la respuesta clínica algo superior; además, se demostró que la administración de un segundo ciclo de esta terapia proporcionó unas tasas de erradicación del 92,8%. Estos datos contrastan con las menores tasas de erradicación (60-86%) que consiguen las fluoroquinolonas en monoterapia [21]. Además, Magri et al [24] demostraron que la terapia combinada reduce significativamente los síntomas tanto durante el tratamiento como en el periodo de seguimiento.

Por último, se debe seleccionar una pauta antibiótica que tenga actividad frente a bacterias grampositivas cuando se detecta en los cultivos. Una alternativa muy válida podría ser moxifloxacino, aunque es frecuente que no se ensaye en los laboratorios, tal y como ocurrió en nuestra serie. Hurtado et al [25] demostraron que moxifloxacino alcanza concentraciones prostáticas superiores a levofloxacino, teniendo una alta ratio AUC/CMI a este nivel. Otro antibiótico plausible sería linezolid, una con actividad exclusiva frente a grampositivos. En nuestro trabajo, la tasa de resistencia de *E. faecalis* muy baja (1,68%), pudiendo ser considerado como una alternativa válida en las PCB causadas por dicho microorganismo. Sin embargo, no sería un antibiótico válido para una terapia empírica puesto que no actuaría sobre las bacterias gramnegativas. Por tanto, el tratamiento que potencialmente reúne todas las condiciones que hemos indicado es la combinación de moxifloxacino y azitromicina, reservando a fosfomicina como tratamiento de elección de las PCB causadas por bacterias multirresistentes, como las enterobacterias productoras de BLEEs. Es necesario realizar ensayos clínicos que demuestren la utilidad real de esta combinación, analizando el coste-beneficio, efectos adversos y adherencia terapéutica.

Finalmente, cabe mencionar varios puntos débiles de este trabajo. En primer lugar, el principal inconveniente ha sido el pequeño tamaño muestral (n= 364); debido a ello, solo hemos

podido sacar conclusiones relevantes y significativas en relación con los principales microorganismos aislados: *E. faecalis*, *Ureaplasma* spp. y *E. coli*. Por otra parte, debido a la dificultad, al cambio de paradigma en cuanto a la etiología y a la falta de estandarización de los criterios de inclusión en los distintos trabajos, es posible que las conclusiones obtenidas, sobre todo en relación con la etiología infecciosa no sean absolutas, siendo imperante la revisión de la clasificación de los pacientes con síntomas prostáticos crónicos, entendiendo que una gran cantidad de pacientes históricamente incluidos en la categoría III son realmente pacientes NIH-II, puesto que ya conocemos el papel de las bacterias atípicas como agentes directamente implicados en la etiología de esta entidad. Otra limitación sería la posible etiología falsa por microorganismos que forman parte de la microbiota habitual de la piel y por lo tanto pueden estar presentes en el semen. Sin embargo, nuestro laboratorio dispone de manuales propios para la correcta recogida de muestras, en unos pacientes con urocultivos simultáneos negativos.

En conclusión, en nuestra población, *E. faecalis* se erige como el principal microorganismo en BPS, siendo *Ureaplasma* spp. el segundo. Las resistencias antibióticas de *E. faecalis* a ciprofloxacino y levofloxacino que hemos encontrado son ligeramente inferiores a las halladas en la literatura, destacando la elevada sensibilidad a linezolid. Además, tanto *E. coli* como *E. faecalis*, mostraron una baja tasa de resistencia a fosfomicina.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses

BIBLIOGRAFÍA

1. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010;50:1641-52. doi: 10.1086/652861
2. Krieger JN, Nyberg L, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. 1999;282:236-7. doi: 10.1001/jama.282.3.236
3. Nickel JC, Shoskes D, Wang Y, Alexander RB, Fowler JE, Zeitlin S, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol. 2006;176:119-24. doi: 10.1016/S0022-5347(06)00498-8
4. Wise GJ, Shteynshlyuger A. Atypical infections of the prostate. Curr Prostate Reports. 2008;6:86-93.doi:10.1007/s11918-008-0014-2
5. Naber KG, Roscher K, Botto H, Schaefer V. Oral levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis. Int J Antimicrob Agents. 2008;32:145-53. DOI: 10.1016/j.ijantimicag.2008.03.014
6. Stamatiou K, Pierris N. Mounting resistance of uropathogens to antimicrobial agents: A retrospective study in patients with chronic bacterial prostatitis relapse. Investig Clin Urol. 2017;58:271. DOI: 10.4111/icu.2017.58.4.271
7. Siles-Guerrero V, Cardona-Benavides I, Liébana-Martos C, Vázquez-Alonso F, Expósito-Ruiz M, Navarro-Marí JM, et al. Recent clinical relevance of mono-genital colonization/infection by *Ureaplasma parvum*. Eur J Clin Microbiol Infect Dis. 2020;39:1899-905. DOI: 10.1007/s10096-020-03928-2
8. Ibrahim NMR. Microbiological profile and antibiotic sensitivity pattern of bacteria isolated from patients with chronic bacterial prostatitis. Eur J Mol Clin Med. 2021;8:1781-9. https://ejmcm.com/article_7986_45e02e71ead656a408564c5a9ecf4ed1.pdf
9. Wagenlehner FME, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. Clin Microbiol Infect. 2006;12 Suppl 3:67-80. DOI: 10.1111/j.1469-0691.2006.01398.x
10. Cai T, Mazzoli S, Meacci F, Boddi V, Mondaini N, Malossini G, et al. Epidemiological features and resistance pattern in uropathogens isolated from chronic bacterial prostatitis. J Microbiol. 2011;49:448-54. DOI: 10.1007/s12275-011-0391-z
11. Brunner H, Weidner W, Schiefer HG. Studies on the role of *Ureaplasma urealyticum* and *Mycoplasma hominis* in prostatitis. J Infect Dis. 1983;147:807-13. DOI: 10.1093/infdis/147.5.807
12. Choi YS, Kim KS, Choi SW, Kim S, Bae WJ, Cho HJ, et al. Microbiological etiology of bacterial prostatitis in general hospital and primary care clinic in Korea. Prostate Int. 2013;1:133-8. DOI: 10.12954/PI.13023
13. Skerk V, Krhen I, Schonwald S, Cajic V, Markovinovic L, Roglic S, et al. The role of unusual pathogens in prostatitis syndrome. Int J Antimicrob Agents. 2004;24:53-6. DOI: 10.1016/j.ijantimicag.2004.02.010
14. Bielecki R, Ostaszewska-Puchalska I, Zdrodowska-Stefanow B, Baltaziak M, Skawrońska M, Sokołowska M. The presence of *Chlamydia trachomatis* infection in men with chronic prostatitis. Cent Eur J Urol. 2020;73:362-8. DOI: 10.5173/ceju.2020.0040
15. Seo Y, Lee G. Antimicrobial Resistance Pattern in *Enterococcus faecalis* Strains Isolated From Expressed Prostatic Secretions of Patients With Chronic Bacterial Prostatitis. Korean J Urol. 2013;54:477-81. DOI: 10.4111/kju.2013.54.7.477
16. Heras-Cañas V, Gutiérrez-Soto B, Almonte-Fernández H, Lara-Oya A, Navarro-Marí JM, Garrido-Frenich A, et al. Actividad y concentraciones de antibióticos en muestras clínicas de pacientes con prostatitis crónica bacteriana. Actas Urol Esp. 2017; 41:631-8. DOI: 10.1016/j.acuro.2017.03.008
17. Charalabopoulos K, Karachalios G, Baltogiannis D, Charalabopoulos A, Giannakopoulos X, Sofikitis N. Penetration of antimicrobial agents into the prostate. Chemotherapy. 2003;49:269-79. DOI: 10.1159/000074526
18. Wagenlehner FME, Weidner W, Sörgel F, Naber KG. The role of antibiotics in chronic bacterial prostatitis. Int J Antimicrob Agents. 2005;26:1-7. doi: 10.1016/j.ijantimicag.2005.04.013.
19. Mendoza-Rodríguez R, Hernández-Chico I, Gutiérrez-Soto B, Navarro-Marí JM, Gutiérrez-Fernández J. Microbial etiology of bacte-

rial chronic prostatitis: systematic review. 2023. Rev Esp Quimioter. 2023 Jan 9. doi: 10.37201/req/099.2022.

20. Bundrick W, Heron SP, Ray P, Schiff WM, Tennenberg AM, Wiesinger A, et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: A randomized double-blind multicenter study. Urology. 2003; 62:537-41. doi: 10.1016/s0090-4295(03)00565-x.
21. Bulitta JB, Kinzig M, Naber CK, Wagenlehner FME, Sauber C, Landersdorfer CB, et al. Population pharmacokinetics and penetration into prostatic, seminal, and vaginal fluid for ciprofloxacin, levofloxacin, and their combination. Chemotherapy. 2011;57:402-16. doi: 10.1159/000329520.
22. Wagenlehner FME, Naber KG. Antimicrobial treatment of prostatitis. Expert Rev Anti Infect Ther. 2003;1:275-82. doi: 10.1586/14787210.1.2.275.
23. Soriano Viladomiu, Mensa Pueyo, J., López Suñé, E., Zboromyrska, Y., Llinares Mondejar, P., & Barberán López, J. (2022). Guía de terapéutica antimicrobiana : 2022: Mensa Gatell. Editorial Antares. ISBN 9788488825315
24. Magri V, Trinchieri A, Ceriani I, Marras E, Perletti G. Eradication of unusual pathogens by combination pharmacological therapy is paralleled by improvement of signs and symptoms of chronic prostatitis syndrome. Arch Ital Urol Androl. 2007;79:93-8. PMID: 17695415
25. Hurtado F, Laureano JV, De A. Lock G, Derendorf H, Dalla Costa T. Enhanced penetration of moxifloxacin into rat prostate tissue evidenced by microdialysis. Int J Antimicrob Agents. 2014; 44:327-33. doi: 10.1016/j.ijantimicag.2014.06.011.

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Shigelosis atendidas en el servicio de urgencias de un hospital regional del sudeste de España: Desde su presencia a la multirresistencia

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RESUMEN

Introducción. En la etiología bacteriana de la diarrea infecciosa aguda grave, exceptuando la causada por *Clostridioides difficile*, la mayor parte presentan un carácter invasor y el tratamiento antibiótico será preciso en situaciones concretas. *Shigella* es un patógeno clásico, en el que es crucial conocer la sensibilidad a distintos antimicrobianos clásicos y alternativos. El objetivo de este trabajo fue analizar la presencia de shigelosis y la tasa de resistencia a los antibióticos.

Métodos. Se realizó un estudio descriptivo-retrospectivo de los informes de shigelosis de los coprocultivos emitidos entre enero de 2016 y abril de 2022.

Resultados. Se observó un total de 34 episodios (16 -47,1%- por *Shigella sonnei*), a partir del 2018. Sólo hubo 2 casos pediátricos. La tasa de resistencia global a azitromicina, trimetoprim-sulfametoxazol y ciprofloxacino fue de 52,9%, 64,7% y 44,1%, respectivamente. El 26,5% fueron resistentes a los 3 grupos de antibióticos. Hubo mayor tasa de resistencia por *S. sonnei*. Destaca la aparición de resistencia a cefalosporinas en los últimos años. Los episodios de shigelosis multirresistente se detectaron entre 2020 (1 por *S. flexneri*) y 2022 (4 por *S. sonnei*).

Conclusiones. Los episodios de shigelosis importada están emergiendo en nuestro medio con una mayor tasa de multirresistencia. En este contexto, los tratamientos empíricos actuales para las enteritis agudas enteroinvasivas corren el riesgo de fracasar, en caso de ser necesarios.

Palabras clave: enteritis, epidemiología, antibióticos, shigelosis.

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Shigellosis attended in the emergency department of a regional hospital in southeastern Spain: from their presence to multiresistance

ABSTRACT

Introduction. In the bacterial etiology of severe acute infectious diarrhea, except that caused by *Clostridioides difficile*, most of them have an invasive character and antibiotic treatment will be necessary in specific situations. *Shigella* is a classic pathogen, in which it is crucial to know the sensitivity to different classic and alternative antimicrobials. The objective of this work was to analyze the presence of shigellosis and the rate of antibiotic resistance.

Methods. A descriptive-retrospective study of the reports of shigellosis of stool cultures issued between January 2016 and April 2022 was conducted.

Results. A total of 34 episodes (16 -47.1%- by *Shigella sonnei*) were observed, as of 2018. There were only 2 pediatric cases. The overall resistance rate to azithromycin, trimethoprim-sulfamethoxazole and ciprofloxacin was 52.9%, 64.7% and 44.1%, respectively. 26.5% were resistant to the 3 groups of antibiotics. There was a higher rate of resistance for *S. sonnei*. The emergence of resistance to cephalosporins in recent years stands out. Episodes of multidrug-resistant shigellosis were detected between 2020 (1 by *S. flexneri*) and 2022 (4 by *S. sonnei*).

Conclusions. The episodes of shigellosis are emerging in our environment with a higher rate of multi-resistance. In this context, current empirical treatments for acute enteroinvasive enteritis are at risk of failure, if necessary.

Keywords: enteritis, epidemiology, antibiotics, shigellosis.

INTRODUCCIÓN

La diarrea infecciosa constituye un grave problema de salud pública a nivel mundial, especialmente en la población infantil. Los casos de diarrea grave son mayoritariamente causados por bacterias [1]. En el caso de *Clostridioides difficile*, aproximadamente el 5% de adultos y hasta el 70% de los lactantes están colonizados por éste, pero únicamente el 25-30% desarrollan enfermedad y, además, las pruebas de diagnóstico no diferencian entre portador e infección [2]. Todo lo contrario, ocurre con el resto de patógenos bacterianos, donde la mayor parte de ellos presenta un carácter invasor intestinal, considerándose primordial conocer su presencia para la orientación diagnóstica y el tratamiento. En especial, para los cuadros de enteritis causados por bacterias multirresistentes, que lamentablemente son cada vez más frecuentes en nuestro medio [3,4].

La shigelosis es una patología infecciosa intestinal aguda, producida por el género *Shigella*. Se trata de una bacilo Gram negativo que comprende cuatro especies: *S. dysenteriae, S. boydii, S. sonnei* y *S. flexneri*, siendo estas dos últimas las más frecuentes [5]. El género *Shigella* es altamente contagioso [6] y se transmite principalmente por vía feco-oral a través de contacto directo persona-persona o por alimentos o agua contaminada [7]. La presencia de un plásmido de gran virulencia (pINV) que codifica un sistema de secreción de tipo III respalda la invasión de *Shigella* a las células epiteliales del colon, la generación de inflamación y necrosis localizadas, que combinadas con la expresión de ciertos genes genera síntomas característicos como calambres abdominales y diarrea mucoide [8,9].

Respecto al tratamiento de la diarrea, tanto dirigido como empírico, solo será preciso en casos concretos con el fin de acortar la duración de la enfermedad, disminuir la transmisión y evitar, en la medida de lo posible, las complicaciones. Por lo tanto, es crucial estudiar el comportamiento frente a distintos antimicrobianos para un mejor tratamiento de los cuadros infecciosos que producen [10-12].

El aumento de la resistencia a fármacos previos de primera línea [13,14] han convertido al ciprofloxacino, la azitromicina y la ceftriaxona en los fármacos de elección para el tratamiento empírico, pero ahora están surgiendo resistencias a estos nuevos fármacos. Un solo clado de *S. sonnei* extendido en el sur de Asia parece estar impulsando la diseminación internacional de organismos resistentes a ciprofloxacino [15], causando importaciones y estableciendo la transmisión en lugares con baja endemicidad, incluidos Australia, Europa y EE. UU. [16]. La resistencia a la azitromicina apareció hace más de una década [17] y se está propagando globalmente, particularmente entre hombres que tienen sexo con hombres (HSH) y poblaciones VIH seropositivas [18]. El aumento de la resistencia a las cefalosporinas de tercera generación en Asia podría dejar pocas opciones para una terapia eficaz [19], por lo que se ha declarado que la *Shigella* resistente a los antibióticos es una amenaza grave que requiere nuevas intervenciones.

El objetivo de este trabajo fue realizar una revisión anualizada de los episodios de shigelosis en los últimos 4 años, analizando su perfil de resistencia a los antibióticos.

MATERIAL Y MÉTODOS

Se llevó a cabo un estudio descriptivo-retrospectivo de los resultados registrados en nuestro SIL de los coprocultivos de episodios de shigelosis entre el 1 de enero de 2016 y el 30 abril del 2022. El ámbito geográfico fue la provincia de Granada y el ámbito poblacional fue el área de referencia del Hospital Universitario Virgen de las Nieves, con una población de referencia básica de 330.486 habitantes, pero que tiene una actividad asistencial de tercer nivel. En nuestro trabajo se definió como caso todo paciente procedente exclusivamente del servicio de urgencias con clínica de diarrea aguda y coprocultivo positivo para *Shigella*, excluyéndose el resto de los casos con enterobacterias productoras de enteritis invasiva. Para la obtención del diagnóstico etiológico de *Shigella*, las muestras fueron procesadas inicialmente siguiendo un protocolo estricto de trabajo establecido por el laboratorio para las heces. Para el transporte se empleó la refrigeración en frío si fue necesario. No se empleó ningún método de cribado previo a la siembra, por lo que todas las heces no sólidas fueron cultivadas. No se calculó tamaño muestral, pues se seleccionaron todos los registros de los cuatro años que cumplían los criterios de inclusión y exclusión.

Para el coprocultivo se siguieron procedimientos previamente descritos [20]. Brevemente, los medios de cultivo fueron agar Campy-BAP, Hektoen, XLD, CIN y MacConkey sorbitol (BD, Madrid, España) con detección de la toxina siga (SHIGA TOXIN QUIK CHEK ™, TechLab, Blacksburg, VA, EEUU). Todos los medios se incubaron a 37ºC en aerobiosis, a excepción del medio Campy-BAP en microaerofilia, a 42ºC y el agar CIN a 30ºC. El crecimiento de las bacterias se evaluó a las 18 horas y a las 48 horas. Una vez realizada la identificación presuntiva mediante los medios de cultivo, se procedió a realizar una identificación definitiva mediante MALDI-TOF Biotyper (Becton Dickinson, Madrid, España), para la mayoría de las enterobacterias enteroinvasivas, apoyándose además en el sistema MicroScan (Beckman Coulter, Barcelona, España). Este último se utilizó para el diagnóstico definitivo de *Shigella,* cuando la identificación por MALDI-TOF fue *E. coli*, debido a las similitudes genéticas con *Shigella* [21], donde mediante pruebas bioquímicas, se identificó *S. sonnei* y *Shigella* spp. para el resto de las especies. Para el análisis de las tasas de resistencia se analizaron los antibióticos recomendados para el tratamiento de la shigelosis, según la Guía para el tratamiento de la Shigelosis de la Organización Mundial de la Salud (OMS) [22], ciprofloxacino, azitromicina, cefotaxima, trimetoprim-sulfametoxazol, ampicilina y gentamicina. Todos ellos fueron testados mediante el sistema de microdilución en caldo MicroScan (Beckman Coulter, Barcelona, España); con excepción de azitromicina, donde la concentración mínima inhibitoria fue determinada mediante gradiente de difusión (MIC Test Strip, Liofilchem®, Italia) según instrucciones del fabricante. Los resultados se interpretaron siguiendo las guías del Comité Europeo de Pruebas de Sensibilidad a los Antimicrobianos (EUCAST, 2022) [23].

Aquellos aislados que presentaron resistencia a cefalosporinas de 3ª generación fueron incluidos para el estudio genotípico, que consistió en la secuenciación de alto rendimiento del genoma completo mediante la preparación de librerías pair-end, usando el kit comercial Nextera™ DNA Flex Library Preparation Kit (Illumina Inc, San Diego, CA, EE. UU.) y secuenciación en el equipo NextSeq (Illumina). El ADN se extrajo con el sistema automatizado Maxwell RSC (Promega, Madison, Wisconsin, EE. UU.). El ensamblado de las secuencias obtenidas se realizó utilizando SPAdes 3.15.4 y PROKKA v1.12. Para el análisis de las relaciones filogenéticas se empleó el software Ridom SeqSphere+ vs. 6.0.2 usando el esquema definido para *Escherichia coli* (2.528 alelos) y estableciendo un punto de corte de 10 alelos para la detección de agrupamientos.

Se realizó un análisis descriptivo de los datos, en el que se calcularon las frecuencias absolutas y relativas para las variables categóricas, y las medidas de tendencia central y dispersión para las numéricas. Los datos se analizaron con el programa IBM® SPSS® Statistics. El protocolo del estudio se realizó con arreglo a la Declaración de Helsinki y la Comisión de Ética e Investigación Sanitaria de los Centros Sanitarios Hospitalarios y Distritos de Atención Sanitaria. Se trató de un estudio no intervencionista. Se realizaron los análisis de datos utilizando una base de datos anónima. La Unidad de Gestión Clínica de Microbiología Clínica del Hospital Universitario Virgen de las Nieves (Granada, España) fue la entidad que concedió permiso para acceder y utilizar los datos.

RESULTADOS

Shigelosis en nuestro medio durante los años 2016-2022: tasas de resistencia global, combinada y anualizada. El número de episodios de shigelosis atendidos en el servicio de urgencias de nuestro hospital, entre enero del 2016 y abril del 2022, alcanzaron un total de 34 casos. Entre el año 2016 y 2017 no se registraron episodios de shigelosis, siendo todos ellos a partir del 2018. De todos los sujetos incluidos, 28 (82%) fueron varones y 6 (18%) mujeres. Solo hubo 2 casos pediátricos, siendo el resto adultos, con una media de edad de 36,2 años. En cuanto a la especie productora de la shigelosis, 16 (47,1%) se debieron a la especie *S. sonnei,* mientras que los 18 casos restantes (52,9%) correspondieron a otras especies de *Shigella*.

En la Tabla 1 se presenta la tasa de resistencia global a los grupos de antibióticos más representativos para el tratamiento de la shigelosis. La tasa de resistencia global para azitromicina, trimetoprim-sulfametoxazol y ciprofloxacino fue de 52,9%, 64,7% y 44,1% respectivamente. Mientras que el 26,5% fueron resistentes a los tres antibióticos. La CMI de azitromicina en los cuatro aislados de *S. sonnei* del brote fue superior a 256 mg/L. En cuanto a la diferenciación de especies, cabe destacar la mayor tasa de resistencia en todos los grupos antibióticos presentada por *S. sonnei* respecto al resto de especies de *Shigella* spp. Mientras que la menor tasa de resistencia fue para gentamicina en ambos grupos.

Clínica de los episodios de shigelosis multirresistente. Los episodios de shigelosis multirresistente no importada registrados en nuestro hospital, se detectaron entre el año 2020 y 2022. El primer caso se debió a un caso de *S. flexneri,* en el año 2020. Mientras que durante los años 2021 y 2022 se dieron cuatro casos más de shigelosis multirresistente, causados por *S. sonnei*. A continuación, se detallan por separado los cinco casos clínicos descritos. En la Tabla 2 se resumen las características clínicas de los cuadros de shigelosis multirresistente presentados. Los resultados del análisis de genomas completos se reflejan en la Figura 1. Únicamente se incluyeron las secuencias de *S. sonnei* al disponer de un único aislado de *S. flexneri*. Como se observa en la figura, los cuatro aislados se agrupaban en un único *cluster* definido con un punto de corte de siete alelos. Tomando como referencia el aislado 20212666 (varón 25 años) el aislado más distante genéticamente (siete alelos) sería el 20220157 (varón 21 años) seguido del 20212667 (varón 36 años) con cuatro alelos de diferencia y del 20220582 (varón 26 años) con un alelo de diferencia. En la figura se muestran los determinantes genéticos de resistencia observando una correlación del 100% entre el perfil fenotípico y el perfil genotípico.

i) Shigelosis por *S. flexneri* multirresistente

Caso 1

Se trató de un varón de 29 años, procedente de Honduras, con última visita a su país hacía 12 meses y sin viajes al extranjero desde entonces. Acudió a Urgencias porque, estando previamente sano y tras la ingesta de pollo, en mal estado según reconoció, comenzó con un cuadro de menos de 24 horas de evolución de deposiciones líquidas, sanguinolentas, de hasta más de siete al día, dolor abdominal mesogástrico continuo, que no cedía a analgésicos convencionales, y sensación distérmica, con escalofríos y malestar general, con regular estado general. La temperatura corporal fue 37,3 °C. El abdomen era doloroso a la palpación en mesogastrio, hipocondrio derecho y fosa iliaca izquierda, con aumento de ruidos intestinales. En la analítica de Urgencias destacó una proteína C reactiva de 133 mg/l, con hiponatremia (131 mEq/l) e hipopotasemia (3,1 meq/l) leves. Ante la situación de estabilidad clínica y buena tolerancia por vía oral, fue dado de alta con tratamiento antibiótico empírico (metronidazol 500 mg/8 h durante siete días y azitromicina 500 mg/24 h durante seis días). La sintomatología se resolvió en pocos días y en la revisión a las tres semanas se constató mejoría clínica y normalización de iones y PCR. El estudio microbiológico puso de manifiesto que era productora de CTX-M-15 y resistente *in vitro* a cefalosporinas de hasta cuarta generación, ciprofloxacino y cotrimoxazol.

ii) Shigelosis por *S. sonnei* multirresistente

Caso 2

Varón de 25 años, con antecedentes personales de hepatitis A pasada y condilomas acuminados por VPH tanto en pene como en la región perianal, por conductas sexuales de riesgo. Acudió a urgencias por aparición de dolor abdominal tipo cóli-

Tabla 1 **Resistencia general a los diferentes antibióticos recomendados para el tratamiento de la shigelosis**

	n	AMP	CTX	CEP	CIP	AZI	SXT	GEN
S. sonnei	16	10/16 (62,5%)	11/16 (68,7%)	4/16 (25%)	11/16 (68,7%)	7/10 (70%)	13/16 (81,2%)	1/16 (6,2%)
Otras *Shigella* spp.	18	5/18 (27,8%)	2/18 (11,1%)	1/18 (5,5%)	5/18 (27,8%)	2/7 (28,6%)	9/18 (50%)	0/18 (0%)

AMP: ampicilina; CTX: cefotaxima; CEP: cefepime; CIP: ciprofloxacino; SXT: trimetoprim-sulfametoxazol; GEN: gentamicina.

co en los 4 días previos con sensación distérmica, acompañado de numerosas deposiciones diarreicas de consistencia líquida sin productos patológicos, así como sensación de náuseas y vómitos de aspecto bilioso vómitos, y fiebre de 39ºC. En la exploración se apreció un importante empeoramiento del estado general, con sequedad de mucosas, hipotensión, dolor abdominal persistente a la palpación generalizada. En el control analítico destacó el aumento de reactantes de fase aguda (PCR y procalcitonina) con hemograma normal. Se le realizó una ecografía abdominal de urgencia cuya conclusión fue de "marcada hepatoesplenomegalia, con hallazgos de colitis de etiología inespecífica, sin presentar signos de colecistitis aguda". Debido a la no mejoría del paciente tras 24 horas en el área de observación, a pesar de tratamiento de soporte, se decidió ingresar en planta de Digestivo. Tras 3 días de ingreso, el paciente mejoró siendo dado de alta con recomendaciones dietéticas, tratamiento sintomático, y antibioticoterapia con ciprofloxacino 500mg/12 horas durante 4 días y metronidazol 500mg/8 horas. Desde el punto de vista microbiológico, las heces dieron negativo a la toxina de *Clostridioides difficile*, hemocultivos negativos y en el coprocultivo se aisló *S. sonnei*. El paciente mejoró del cuadro clínico no volviendo a consultar por dicho motivo.

Caso 3

Varón de 36 años, sin antecedentes personales de interés. Acudió a urgencias por referir aparición de dolor abdominal tipo cólico, desde hace 2 días, acompañado de náuseas, vómitos de tipo alimenticio y deposiciones diarreicas de consistencia acuosa el mismo día de la consulta, así como aparición de fiebre de 38,5ºC. Su pareja sexual (varón) tuvo síntomas similares 2 semanas antes de este evento, A la exploración física el paciente se encontró hemodinámicamente estable con dolor abdominal a la palpación en mesogastrio e hipocondrio derecho. En la analítica el paciente presentó una hiperbilirrubinemia discreta a expensas de bilirrubina indirecta, mientras que el hemograma mostró una leucocitosis con neutrofilia. Dado el buen estado general, el paciente fue dado de alta con recomendaciones dietéticas, ciprofloxacino 500 mg /12 horas 5 días, tratamiento sintomático y control por su médico de atención primaria para conocer los resultados del coprocultivo. Una semana después, su médico informó al paciente del crecimiento de *S. sonnei* en el coprocultivo, sin ofrecer cambio de pauta antibiótica, dada la resolución del cuadro clínico.

Caso 4

Varón de 21 años, sin antecedentes personales ni epidemiológicos de interés, salvo conductas sexuales de riesgo con hombres. Acudió a urgencias por un cuadro de diarrea de 5 días de evolución de unas 5-6 deposiciones diarias, algunas de ellas con trazas de restos hemáticos, acompañadas de dolor abdominal difuso y fiebre de 38,2ºC, con empeoramiento del estado general en los últimos días. A la exploración física presentó dolor abdominal a la palpación en hipogastrio, sin más hallazgos de interés. La analítica presentó una discreta hiperbilirrubinemia a expensas de bilirrubina indirecta, con resto de analítica y hemograma normal. Tras unas horas de observación con tratamiento de soporte se decidió el alta domiciliaria, con ciprofloxacino 500 mg/12 horas durante cinco días, tratamiento sintomático y control por su médico de atención primaria para conocer resultados del coprocultivo. Tras cinco días de tratamiento, el paciente acudió a su médico de atención primaria, por no mejoría de la clínica, que, sin poder acceder a los resultados del coprocultivo, cambió a amoxicilina/clavulánico 1 comprimido /8 horas durante cinco días. A la semana siguiente, el paciente acudió de nuevo a las urgencias por presentar persistencia de la diarrea de aspecto verdoso y maloliente, así como fiebre de 38,5ºC con dolor abdominal asociado. En la exploración presentó dolor abdominal a la palpación en fosa ilíaca y flanco derecho, presentando una analítica con bioquímica y hemograma normal. Finalmente, fue dado de alta y derivado a consultas externas de la unidad de Enfermedades Infecciosas donde se le cambió el tratamiento a azitromicina 500 mg /24 horas durante 3 días. A la semana, en cita de revisión, el paciente refirió encontrarse mucho mejor y sin diarrea.

Caso 5

Varón 26 años, sin antecedentes personales ni epidemiológicos de interés, que acudió a urgencias por un cuadro de dolor abdominal difuso desde hace 4 días, con fiebre asociada de 38ºC y diarrea de unas 4-5 deposiciones al día, de consistencia líquida sin sangre ni otros productos patológicos, sin nauseas ni vómitos. A la exploración física el paciente se encontró con buen estado general, exploración física normal, salvo dolor abdominal a la palpación profunda de manera difusa. Analíticamente el paciente no presentó alteraciones llamativas, con hemograma normal. El paciente no precisó de analgesia ni tratamiento sintomático, por lo que se dio de alta domiciliaria con recomendaciones dietéticas y tratamiento sintomático si lo precisara. Además, se le remitió a su médico de atención primaria para consultar los resultados del coprocultivo. Los resultados fueron positivos para *S. sonnei,* pero el paciente no precisó de antibioticoterapia para resolver el cuadro clínico.

Tabla 2 **Características clínicas de shigelosis multirresistente en nuestra serie de casos.**

	Caso 1	Caso 2	Caso 3	Caso 4	Caso 5
Especie	*S. flexneri*	*S. sonnei*	*S. sonnei*	*S. sonnei*	*S. sonnei*
Año	2020	2021	2021	2022	2022
Sexo	Varón	Varón	Varón	Varón	Varón
Edad	29 años	25 años	36 años	21 años	26 años
Factores de riesgo	No conocidos	HSH	HSH	HSH	No conocidos
Fiebre/febrícula	Sí	Sí	Sí	Sí	Sí
Diarrea sanguinolenta	Sí	No	No	Sí	No
Dolor abdominal	Sí	Sí	Sí	Sí	Sí
Inestabilidad hemodinámica	No	Sí	No	No	No
PCR elevada	Sí	Sí	Sí	Sí	Sí
Leucocitosis	No	No	Sí	No	No
Hiperbilirrubinemia	No	No	Sí	Sí	No
Hospitalización	No	Sí	No	No	No
Tratamiento/Curación	Autorresolutiva	Autorresolutiva	Autorresolutiva	Autorresolutiva	Autorresolutiva

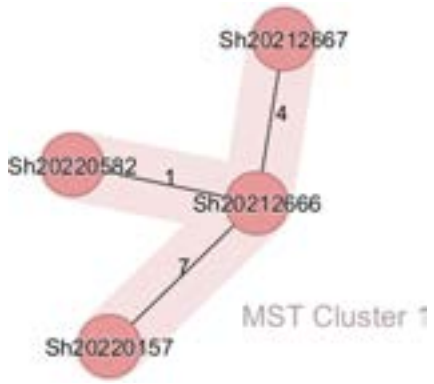
HSH: Hombres que tienen sexo con hombres; PCR: proteína C reactiva

DISCUSIÓN

Según la OMS [24], la diarrea es la segunda causa de muerte en niños menores de 5 años y representa un problema de mayor entidad en países en vías de desarrollo. En los países en vías de desarrollo se han aislado con más frecuencia distintas cepas de *E. coli* [25]. Mientras que otro patógeno relevante en estos países es *Shigella* spp., fundamentalmente *S. flexneri*, tanto en diarrea con sangre, como en diarrea acuosa y, especialmente, en casos de disentería. Los casos diagnosticados a lo largo de los años permanecen estables, como se puede observar al comparar los datos de distintos estudios [26,27]. Además, *Shigella* spp. se ha notificado como causa más frecuente de diarrea con sangre en estudios de países industrializados [28]. A diferencia de los países en vías de desarrollo, en los países desarrollados se ha aislado fundamentalmente *S. sonnei,* según la revisión de Humphries et al [10]. En dicho trabajo, únicamente aparecieron 5 artículos en la revisión que hacen referencia a nuestra área geográfica, uno de ellos (año 1998) hace alusión a la diarrea del viajero [29], con lo cual disponemos únicamente de 4 trabajos para sacar conclusiones.

S. sonnei representa hasta el 80% de todas las infecciones por *Shigella* en el mundo desarrollado, particularmente en América del Norte y Europa [30]. También ha contribuido significativamente a brotes de origen alimentario, en diversos países como Estados Unidos [31,32], Canadá [33], España [34], Japón [35], Dinamarca [36], entre otros países. Sin embargo, la tendencia mundial de las infecciones por *S. sonnei* ha cambiado debido a elementos multifactoriales basados en la geografía, el clima, las relaciones huésped-patógeno y las estrategias de control correspondientes. En España hay publicado un caso autóctono, en 2011, correspondiente a *S. sonnei* [37]; otros casos por *S. sonnei* y *S. flexneri* entre el año 2015 y 2019, y más recientemente un caso de *S. flexneri*, en nuestro medio, en el año 2020 [38]. Cabe destacar que en 2016 y 2017 no se detectaron casos de shigelosis en nuestro medio, aunque nuestro laboratorio no ha cambiado los procedimientos de detección de este microorganismo a lo largo del tiempo. Sólo hay que destacar que el Área de Salud de Granada estudiada en nuestro laboratorio ha cambiado desde 2016 hasta hoy, en el sentido de un aumento de los episodios más graves estudiados en el Servicio de Urgencias de nuestro hospital.

En cuanto a la resistencia a antibióticos, recientemente se han identificado tres linajes principales de *S. sonnei* (I, II, III). *S. sonnei* evolucionó rápidamente desde Europa y se propagó como linaje único resistente a múltiples fármacos (MDR) a otros continentes predominantemente [39]. El número de episodios de enteritis por patógenos multirresistentes están aumentado en nuestro medio [38]. Los aislamientos de *Shigella* en muchos países han adquirido rasgos de resistencia que conducen a la ineficacia de las cefalosporinas para el tratamiento de algunos pacientes [40-42]. Dentro de este fenómeno de multirresistencia, destaca el grupo de HSH, donde ya se han descrito otras series de shigelosis multirresistente en Australia [43], Francia [44], Reino Unido [45] y España [46]. Además, el grupo HSH tienen más posibilidades de ser hospitalizado y recibir antibióticos, lo que indica que sus infecciones son potencialmente más graves [45], tal y como sucedió en nuestro *Caso 2*, donde el paciente requirió de ingreso hospitalario por la inestabilidad hemodinámica sufrida. Así mismo, después de la fase aguda de



Ridom SeqSphere+ MST for 4 Samples based on 2528 columns, pairwise ignoring missing values. Distance based on columns from E. coli MLST Warwick (7), E. coli MLST Pasteur (8), E. coli cgMLST (2513)

MST Cluster distance threshold: 10

Nodes colored by column: ST Warwick (ST-152)

E. coli cgMLST Complex Type / Clustering Distance: 10

Sample ID	ST Warwick	Streptomycin	Cephalosporin	Erythromycin	Telithromycin	Tylosin
Sh20212666	152	aadA5	blaCTX-M-27 (ESBL)	erm(B) / mph(A)	erm(B) / mph(A)	erm(B) / mph(A)
Sh20212667	152	aadA5 / aph(3'')-Ib / aph(6)-Id	blaCTX-M-27 (ESBL)	erm(B) / mph(A)	erm(B) / mph(A)	erm(B) / mph(A)
Sh20220157	152	aadA5 / aph(3'')-Ib / aph(6)-Id	blaCTX-M-27 (ESBL)	erm(B) / mph(A)	erm(B) / mph(A)	erm(B) / mph(A)
Sh20220582	152	aadA5	blaCTX-M-27 (ESBL)	erm(B) / mph(A)	erm(B) / mph(A)	erm(B) / mph(A)

Sample ID	Quinolone/fluoroquinolone	Streptothricin	Sulfonamide	Tetracycline	Trimethoprim
Sh20212666	gyrA_D87G / gyrA_S83L / parC_S80I / qnrB19	sat2	sul1		dfrA1 / dfrA17
Sh20212667	gyrA_D87G / gyrA_S83L / parC_S80I / qnrB19	sat2	sul1 / sul2	tet(A)	dfrA1 / dfrA17
Sh20220157	gyrA_D87G / gyrA_S83L / parC_S80I / qnrB19 / qnrS13	sat2	sul1 / sul2	tet(A)	dfrA1 / dfrA17 / dfrA5
Sh20220582	gyrA_D87G / gyrA_S83L / parC_S80I / qnrB19	sat2	sul1		dfrA1 / dfrA17

Figura 1 | **Análisis de genomas completos de los 4 aislados clínicos de *Shigella sonnei*.**

la infección, el estado de portador puede persistir durante meses y la infección puede reaparecer en meses, incluso con cepas que pertenecen a la misma especie y al mismo serotipo. Por lo que es probable que una combinación de múltiples parejas sexuales, el estado de portador persistente después de la fase aguda de la infección y la evidencia de reinfección recurrente contribuyan a la transmisión sostenida en esta población [47].

El tratamiento de primera línea actualmente recomendado para la shigelosis son las fluoroquinolonas, como el ciprofloxacino; pero debido a su uso común, la resistencia al ciprofloxacino está muy extendida entre las especies de *Shigella* recuperadas en todo el mundo desde principios del siglo XXI, siendo Asia un reservorio probable para el aumento y la propagación de organismos resistentes [48]. Tal resistencia se debe a la acumulación gradual de mutaciones en la girasa y la topoisomerasa, codificadas por los genes cromosómicos *gyrA* y *parC*, respectivamente. Además, los elementos móviles podrían ayudar a dar forma y establecer clones resistentes emergentes [49]. En los últimos años se ha observado un marcado aumento de *S. flexneri* a resistente a azitromicina en las comunidades de HSH de todo el mundo, causado por la propagación de un único sublinaje de esta especie desde 1998 [18]. La resistencia a la azitromicina es inducida por el plásmido móvil pKSR100, que recientemente se demostró que se adquiere en *S. sonnei* [50]. Esto facilitó en gran medida la aparición de nuevas cadenas de transmisión, creando diversos brotes epidémicos de *Shigella* multirresistente circulando en la comunidad HSH. De hecho, de los 5 casos de *Shigella* multirresistente encontrados en nuestro trabajo, 3 sujetos declararon pertenecer al grupo HSH.

Las tasas de resistencia globales descritas en nuestro trabajo, coinciden con las ya publicadas en otra serie española. En Moreno-Mingorance et al. [51] se estudiaron casos de shigelosis por *S. flexneri* y *S. sonnei* (n=70) en hombres del grupo HSH, y se obtuvieron unas tasas de resistencia a trimetoprim-sulfametoxazol (65,7%) y ciprofloxacino (32,8%) similares a las de nuestro entorno. Sin embargo, la resistencia a azitromicina fue mayor (80%) con respecto a la obtenida en nuestra serie (52,9%). Lo que podría explicarse por la falta de datos de azitromicina en nuestro estudio para todos los aislados. No obstante, el vínculo de una mayor resistencia a azitromicina en las shigelosis de pacientes HSH ya era previamente conocido [18]. Con respecto a gentamicina, sin bien presentó buena actividad *in vitro* en nuestra serie, los antibióticos no absorbibles como gentamicina y rifaximina oral, han mostrado resultados variables en la práctica clínica, por lo que su recomendación sería controvertida [52,53].

En cuanto a la evolución de la enfermedad, la shigelosis es una enfermedad autolimitada, y los pacientes suelen recuperarse por completo en 7 a 10 días. Sin embargo, se sabe que la infección causa posibles complicaciones, siendo la más grave la encefalopatía [54]. Por lo tanto, se recomienda el tratamiento antimicrobiano para prevenir complicaciones adicionales, reducir la producción de diarrea y limitar la excreción fecal post-sintomática [55]. En los casos descritos de shigelosis multirresistente en este trabajo, todos ellos tuvieron una buena evolución clínica, siendo finalmente cuadros autorresolutivos. Esto coincide con un estudio recientemente publicado sobre diarrea en población pediátrica, donde se encontró que la duración de la hospitalización de los pacientes infectados por *Shigella* fue similar, independientemente del perfil de multirresistencia [56].

La multirresistencia probablemente suponga una amenaza más significativa para ciertos grupos de alto riesgo, incluidos los pacientes desnutridos, ancianos e inmunodeprimidos. Este último grupo, supone una preocupación cada vez mayor para la shigelosis multirresistente, ya que están aumentando los casos de HSH en pacientes VIH positivos, donde los cuadros clínicos son de mayor gravedad [57]. Finalmente, hay que destacar que nuestros aislados multirresistentes son del mismo clon que la alerta sanitaria notificada por el sistema de vigilancia epidemiológica del Hospital Universitario Virgen del Rocío (Sevilla, España) [46]. Esta alerta a su vez estaba relacionada con la alerta emitida por el Centro Europeo de Prevención y Control de las Enfermedades (ECDC) en enero de 2022 en la que se informaba de un aumento de los casos de shigelosis causada por *S. sonnei* multirresistente principalmente en HSH. La comparación de los cinco genomas de este estudio con los genomas de referencia puestos a disposición por el ECDC (datos no mostrados) pone de manifiesto la inclusión de estos casos en el mismo *cluster* genético con una diferencia de un máximo de cuatro alelos, así como la presencia del mismo plásmido IncFII portados del gen $bla_{\text{CTX-M-27}}$ lo que pone de manifiesto la dispersión de este clon.

Entre las limitaciones más importantes de nuestro trabajo tenemos el hecho de no haber dispuesto de la CMI para azitromicina en un gran número de aislados. En cuanto a la identificación de especie, tan solo se tuvo identificada la especie *S. sonnei*, para la mayoría de los casos, englobando al resto de aislados en el grupo de otras especies de *Shigella*.

CONCLUSIONES

Nuestros datos actuales ponen de manifiesto que los casos se shigelosis están emergiendo en nuestro medio, con una mayor tasa de multirresistencia, en especial en el grupo HSH. En este contexto, los tratamientos empíricos actuales para las enteritis agudas enteroinvasivas corren el riesgo de fracasar, entre los que se incluyen ciprofloxacino, azitromicina y las cefalosporinas de tercera generación, destacando en pacientes inmunocomprometidos, especialmente porque las opciones de tratamiento estarán limitadas por el plásmido IncFII multirresistente. Esto supone una continua amenaza para la salud pública tanto en España como en el resto del mundo. Por lo que se requieren medidas multidisciplinarias urgentes de salud pública centradas en la detección precoz de la infección y prevención de la transmisión, con objeto de paliar la crisis de resistencia a los antimicrobianos. Esto plantea preocupaciones sobre la capacidad de controlar la propagación de la infección por *Shigella* resistente y destaca la necesidad de intensificar la vigilancia de la shigelosis, para minimizar el riesgo de infección a través de la exposición oral fecal durante las actividades sexuales, entre otras.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

BIBLIOGRAFÍA

1. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. 2017;65(12):1963–73. doi: 10.1093/cid/cix959.
2. Czepiel J, Dróżdż M, Pituch H, Kuijper EJ, Perucki W, Mielimonka A, et al. Clostridium difficile infection: review. Eur J Clin Microbiol Infect Dis. 2019;38(7):1211–21. doi: 10.1007/s10096-019-03539-6.
3. Guzmán-Martín JL, Navarro-Marí JM, Expósito-Ruiz M, Gutiérrez-Fernández J. Nalidixic acid surrogate test for susceptibility to ciprofloxacin in Salmonella. Revisiting the question. J Med Microbiol. 2018;67(7):965–7. doi: 10.1099/jmm.0.000755.
4. Aparicio-Gómez JA, Herrera-López S, Gutiérrez-Fernández J. The first description of the extended-spectrum beta-lactamase blaSHV-12 gene in a Salmonella monophasic Typhimurium strain isolated from acute gastroenteritis in a kidney transplant recipient in Southeast Spain. Rev Espanola Enfermedades Dig. 2017;109(5):391–2. doi: 10.17235/reed.2017.4617/2016.
5. Chiou CS, Izumiya H, Kawamura M, Liao YS, Su YS, Wu HH, et al. The worldwide spread of ciprofloxacin-resistant Shigella sonnei among HIV-infected men who have sex with men, Taiwan. Clin Microbiol Infect. 2016; 22(4):383.e11-383.e16. doi: 10.1016/j.cmi.2015.12.021.
6. DuPont HL, Levine MM, Hornick RB, Formal SB. Inoculum size in shigellosis and implications for expected mode of transmission. J Infect Dis. 1989;159(6):1126–8. doi: 10.1093/infdis/159.6.1126.
7. Murray K, Reddy V, Kornblum JS, Waechter H, Chicaiza LF, Rubinstein I, et al. Increasing Antibiotic Resistance in Shigella spp. from Infected New York City Residents, New York, USA. Emerg Infect Dis. 2017;23(2):332–5. doi: 10.3201/eid2302.161203.
8. Schroeder GN, Hilbi H. Molecular pathogenesis of Shigella spp.: controlling host cell signaling, invasion, and death by type III secretion. Clin Microbiol Rev. 2008;21(1):134–56. doi: 10.1128/

CMR.00032-07.

9. Yang F, Yang J, Zhang X, Chen L, Jiang Y, Yan Y, et al. Genome dynamics and diversity of Shigella species, the etiologic agents of bacillary dysentery. Nucleic Acids Res. 2005;33(19):6445–58. doi: 10.1093/nar/gki954.
10. Humphries RM, Linscott AJ. Practical Guidance for Clinical Microbiology Laboratories: Diagnosis of Bacterial Gastroenteritis. Clin Microbiol Rev. 2015;28(1):3–31. doi: 10.1128/CMR.00073-14.
11. DuPont HL. Approach to the patient with infectious colitis. Curr Opin Gastroenterol. 2012;28(1):39–46. doi: 10.1097/MOG.0b013e32834d3208.
12. DuPont HL. Persistent Diarrhea: A Clinical Review. JAMA. 2016;315(24):2712–23. doi: 10.1001/jama.2016.7833.
13. Kahsay AG, Muthupandian S. A review on Sero diversity and antimicrobial resistance patterns of Shigella species in Africa, Asia and South America, 2001-2014. BMC Res Notes. 2016;9(1):422. doi: 10.1186/s13104-016-2236-7.
14. Sivapalasingam S, Nelson JM, Joyce K, Hoekstra M, Angulo FJ, Mintz ED. High prevalence of antimicrobial resistance among Shigella isolates in the United States tested by the National Antimicrobial Resistance Monitoring System from 1999 to 2002. Antimicrob Agents Chemother. 2006;50(1):49–54. doi: 10.1128/AAC.50.1.49-54.2006.
15. Chung The H, Rabaa MA, Pham Thanh D, De Lappe N, Cormican M, Valcanis M, et al. South Asia as a Reservoir for the Global Spread of Ciprofloxacin-Resistant Shigella sonnei: A Cross-Sectional Study. PLoS Med. 2016;13(8):e1002055. doi: 10.1371/journal.pmed.1002055.
16. Bowen A, Hurd J, Hoover C, Khachadourian Y, Traphagen E, Harvey E, et al. Importation and domestic transmission of Shigella sonnei resistant to ciprofloxacin - United States, May 2014-February 2015. MMWR Morb Mortal Wkly Rep. 2015;64(12):318–20. PMID: 25837241
17. Boumghar-Bourtchai L, Mariani-Kurkdjian P, Bingen E, Filliol I, Dhalluin A, Ifrane SA, et al. Macrolide-resistant Shigella sonnei. Emerg Infect Dis. 2008;14(8):1297–9. doi: 10.3201/eid1408.080147.
18. Baker KS, Dallman TJ, Ashton PM, Day M, Hughes G, Crook PD, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. Lancet Infect Dis. 2015;15(8):913–21. doi: 10.1016/S1473-3099(15)00002-X.
19. Chang Z, Zhang J, Ran L, Sun J, Liu F, Luo L, et al. The changing epidemiology of bacillary dysentery and characteristics of antimicrobial resistance of Shigella isolated in China from 2004-2014. BMC Infect Dis. 2016;16(1):685. doi: 10.1186/s12879-016-1977-1.
20. Del Valle de Toro A, Santos-Pérez JL, Navarro-Marí JM, Gutiérrez-Fernández J. Epidemiological data description of pediatric patients with diarrhea by Aeromonas spp. and the antibiotic susceptibility of this agent. Rev Argent Microbiol. 2020;52(1):22–6. doi: 10.1016/j.ram.2019.03.003.
21. He Y, Li H, Lu X, Stratton CW, Tang YW. Mass spectrometry biotyper system identifies enteric bacterial pathogens directly from colonies grown on selective stool culture media. J Clin Microbiol. 2010;48(11):3888–92. doi: 10.1128/JCM.01290-10.
22. WHO: The selection and use of essential medicines [cited 2022 May 18]. Available from: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists
23. EUCAST: Clinical breakpoints and dosing of antibiotics [cited 2022 Jul 17]. Available from: https://www.eucast.org/clinical_breakpoints/
24. Enfermedades diarreicas [cited 2022 Jul 14]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/diarrhoeal-disease
25. Fagundes-Neto U, Scaletsky IC. The gut at war: the consequences of enteropathogenic Escherichia coli infection as a factor of diarrhea and malnutrition. Sao Paulo Med J Rev Paul Med. 2000;118(1):21–9. doi: 10.1590/s1516-31802000000100006.
26. Suárez-Hoil GJ, Flores-Abuxapqui JJ, Heredia-Navarrete MR, Puc-Franco MA, Franco-Monsreal J. [Prevalence of enteropathogenic bacteria in children with acute bloody diarrhea]. Bol Med Hosp Infant Mex. 1993;50(3):151–6. PMID: 8442878
27. Niyogi SK. Shigellosis. J Microbiol Seoul Korea. 2005;43(2):133–43.
28. Talan D, Moran GJ, Newdow M, Ong S, Mower WR, Nakase JY, et al. Etiology of bloody diarrhea among patients presenting to United States emergency departments: prevalence of Escherichia coli O157:H7 and other enteropathogens. Clin Infect Dis. 2001;32(4):573–80. doi: 10.1086/318718.
29. Gallardo F, Gascón J, Ruiz J, Corachan M, Jimenez de Anta M, Vila J. Campylobacter jejuni as a cause of traveler's diarrhea: clinical features and antimicrobial susceptibility. J Travel Med. 1998;5(1):23–6. doi: 10.1111/j.1708-8305.1998.tb00451.x.
30. Gu B, Cao Y, Pan S, Zhuang L, Yu R, Peng Z, et al. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of Shigella between Europe-America and Asia-Africa from 1998 to 2009. Int J Antimicrob Agents. 2012;40(1):9–17. doi: 10.1016/j.ijantimicag.2012.02.005.
31. Lee LA, Ostroff SM, McGee HB, Johnson DR, Downes FP, Cameron DN, et al. An outbreak of shigellosis at an outdoor music festival. Am J Epidemiol. 1991;133(6):608–15. doi: 10.1093/oxfordjournals.aje.a115933.
32. Kimura AC, Johnson K, Palumbo MS, Hopkins J, Boase JC, Reporter R, et al. Multistate shigellosis outbreak and commercially prepared food, United States. Emerg Infect Dis. 2004;10(6):1147–9. doi: 10.3201/eid1006.030599.
33. Naimi TS, Wicklund JH, Olsen SJ, Krause G, Wells JG, Bartkus JM, et al. Concurrent outbreaks of Shigella sonnei and enterotoxigenic Escherichia coli infections associated with parsley: implications for surveillance and control of foodborne illness. J Food Prot. 2003;66(4):535–41. doi: 10.4315/0362-028x-66.4.535.
34. Garcia-Fulgueiras A, Sánchez S, Guillén JJ, Marsilla B, Aladueña A, Navarro C. A large outbreak of Shigella sonnei gastroenteritis associated with consumption of fresh pasteurised milk cheese. Eur J Epidemiol. 2001;17(6):533–8. doi: 10.1023/a:1014504305666.
35. Gaynor K, Park SY, Kanenaka R, Colindres R, Mintz E, Ram PK, et al. International foodborne outbreak of Shigella sonnei infection in airline passengers. Epidemiol Infect. 2009;137(3):335–41. doi: 10.1017/S0950268807000064.

36. Muller L, Jensen T, Petersen RF, Mølbak K, Ethelberg S. Imported fresh sugar peas as suspected source of an outbreak of Shigella sonnei in Denmark, April-May 2009. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2009;14(24):19241. doi: 10.2807/ese.14.24.19241-en.
37. Seral C, Gude MJ, Castillo FJ. Emergence of plasmid mediated AmpC β-lactamasas: Origin, importance, detection and therapeutical options. Rev Espanola Quimioter Publicacion Of Soc Espanola Quimioter. 2012;25(2):89–99. PMID: **22707098**
38. Rosales-Castillo A, Pedrosa-Corral I, Gutiérrez-Fernández J. A propos of a new case of shigellosis by a non-imported multiresistant strain. Rev Espanola Enfermedades Dig. 2020;112(3):244. doi: 10.17235/reed.2020.6399/2019.
39. Holt KE, Baker S, Weill FX, Holmes EC, Kitchen A, Yu J, et al. Shigella sonnei genome sequencing and phylogenetic analysis indicate recent global dissemination from Europe. Nat Genet. 2012;44(9):1056–9. doi: 10.1038/ng.2369.
40. Albert MJ, Purohit P, Poirel L, Carter G, Bulach D. Diarrhea in an infant due to Shigella flexneri 1 carrying multiple cephalosporinase-encoding genes. Gut Pathog. 2021;13:18. doi: 10.1186/s13099-021-00413-9.
41. Liu G, Qian H, Tang B, Chen Y, Kang H, Jiang F, et al. Prevalence and characterisation of third-generation cephalosporin-resistant Shigella flexneri isolates from Jiangsu Province, China, 2013-2015. J Glob Antimicrob Resist. 2018;15:283–7. doi: 10.1016/j.jgar.2018.08.012.
42. Rahman M, Shoma S, Rashid H, Siddique AK, Nair GB, Sack DA. Extended-spectrum beta-lactamase-mediated third-generation cephalosporin resistance in Shigella isolates in Bangladesh. J Antimicrob Chemother. 2004;54(4):846–7. doi: 10.1093/jac/dkh413.
43. Ingle DJ, Easton M, Valcanis M, Seemann T, Kwong JC, Stephens N, et al. Co-circulation of Multidrug-resistant Shigella Among Men Who Have Sex With Men in Australia. Clin Infect Dis Off Publ Infect Dis Soc Am. 2019;69(9):1535–44. doi: 10.1093/cid/ciz005.
44. Zayet S, Klopfenstein T, Pierron A, Royer PY, Toko L, Garnier P, et al. Shigella sonnei, an emerging multidrug-resistant sexually transmitted pathogen in Franche-Comté, France. Emerg Microbes Infect. 2021;10(1):1702–5. doi: 10.1080/22221751.2021.1969289.
45. Mitchell HD, Thomson NR, Jenkins C, Dallman TJ, Painset A, Kirwan P, et al. Linkage of Whole Genome Sequencing, Epidemiological, and Clinical Data to Understand the Genetic Diversity and Clinical Outcomes of Shigella flexneri among Men Who Have Sex with Men in England. Microbiol Spectr. 2021;9(3):e0121321. doi: 10.1128/Spectrum.01213-21
46. Ortiz de la Rosa JM, Rodríguez-Villodres Á, Casimiro-Soriguer CS, Ruiz-Pérez De Pipaón M, Briones E, Aznar Fernández M, et al. MDR Shigella sonnei in Spain: an ever-evolving emerging threat? JAC-Antimicrob Resist. 2022;4(5):dlac090. doi: 10.1093/jacamr/dlac090.
47. Allen H, Mitchell HD, Simms I, Baker KS, Foster K, Hughes G, et al. Evidence for re-infection and persistent carriage of Shigella species in adult males reporting domestically acquired infection in England. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2021;27(1):126.e7-126.e13. doi: 10.1016/j.cmi.2020.03.036.
48. Chung The H, Baker S. Out of Asia: the independent rise and global spread of fluoroquinolone-resistant Shigella. Microb Genomics. 2018;4(4). doi: 10.1099/mgen.0.000171.
49. Baker S, The HC. Recent insights into Shigella: a major contributor to the global diarrhoeal disease burden. Curr Opin Infect Dis. 2018;31(5):449–54. doi: 10.1097/QCO.0000000000000475.
50. Baker KS, Dallman TJ, Field N, Childs T, Mitchell H, Day M, et al. Horizontal antimicrobial resistance transfer drives epidemics of multiple Shigella species. Nat Commun. 2018;9(1):1462. doi: 10.1038/s41467-018-03949-8.
51. Moreno-Mingorance A, Espinal P, Rodriguez V, Goterris L, Fàbrega A, Serra-Pladevall J, et al. Circulation of multi-drug-resistant Shigella sonnei and Shigella flexneri among men who have sex with men in Barcelona, Spain, 2015-2019. Int J Antimicrob Agents. 2021;58(3):106378. doi: 10.1016/j.ijantimicag.2021.106378.
52. Islam MR, Alam AN, Hossain MS, Mahalanabis D, Hye HK. Double-blind comparison of oral gentamicin and nalidixic acid in the treatment of acute shigellosis in children. J Trop Pediatr. 1994;40(6):320–5. doi: 10.1093/tropej/40.6.320.
53. Taylor DN, McKenzie R, Durbin A, Carpenter C, Haake R, Bourgeois AL. Systemic pharmacokinetics of rifaximin in volunteers with shigellosis. Antimicrob Agents Chemother. 2008;52(3):1179–81. doi: 10.1128/AAC.01108-07.
54. Afroze F, Ahmed T, Sarmin M, Smsb Shahid A, Shahunja KM, Shahrin L, et al. Risk factors and outcome of Shigella encephalopathy in Bangladeshi children. PLoS Negl Trop Dis. 2017;11(4):e0005561. doi: 10.1371/journal.pntd.0005561.
55. Vinh H, Wain J, Chinh MT, Tam CT, Trang PT, Nga D, et al. Treatment of bacillary dysentery in Vietnamese children: two doses of ofloxacin versus 5-days nalidixic acid. Trans R Soc Trop Med Hyg. 2000;94(3):323–6. doi: 10.1016/s0035-9203(00)90343-2.
56. Duong VT, Tuyen HT, Van Minh P, Campbell JI, Phuc HL, Nhu TDH, et al. No Clinical Benefit of Empirical Antimicrobial Therapy for Pediatric Diarrhea in a High-Usage, High-Resistance Setting. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018;66(4):504–11. doi: 10.1093/cid/cix844.
57. Mohan K, Hibbert M, Rooney G, Canvin M, Childs T, Jenkins C, et al. What is the overlap between HIV and shigellosis epidemics in England: further evidence of MSM transmission? Sex Transm Infect. 2018;94(1):67–71. doi: 10.1136/sextrans-2016-052962.

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Economic burden of skin and skin structure infections due to Gram-positive bacteria in patients on hospital at home-based outpatient parenteral antibiotic therapy (OPAT)

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ABSTRACT

Objective. To describe and quantify resource use and direct health costs associated with skin and skin structure infections (SSSIs) caused by Gram-positive bacteria in adults receiving outpatient parenteral antimicrobial therapy (OPAT), administered by Hospital at Home units (HaH) in Spain.

Material and methods. Observational, multicenter, retrospective study. We included patients of both sexes included in the HaH-based OPAT Registry during 2011 to 2017 who were hospitalized due to SSSIs caused by Gram-positive bacteria. Resource use included home visits (nurses and physician), emergency room visits, conventional hospitalization stay, HaH stay and antibiotic treatment. Costs were quantified by multiplying the natural units of the resources by the corresponding unit cost. All costs were updated to 2019 euros.

Results. We included 194 episodes in 189 patients from 24 Spanish hospitals. The most frequent main diagnoses were cellulitis (26.8%) and surgical wound infection (24.2%), and 94% of episodes resulted in clinical improvement or cure after treatment. The median HaH stay was 13 days (interquartile range [IR]:8-22.7), and the conventional hospitalization stay was 5 days (IR: 1-10.7). The mean total cost attributable to the complete infectious process was €7,326 (95% confidence interval: €6,316-€8,416).

Conclusions. Our results suggest that OPAT administered by HaH is a safe and efficient alternative for the management of these infections and could lead to lower costs compared with hospital admission.

Keywords: Hospital at home, outpatient parenteral antimicrobial therapy (OPAT), cost analysis, skin and skin structure infections (SSSIs)

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Carga económica de la infección de piel y partes blandas por microorganismos grampositivos en pacientes en unidades de hospitalización a domicilio con tratamiento antimicrobiano domiciliario endovenoso (TADE)

Objetivo. Describir y cuantificar el uso de recursos y costes directos sanitarios asociados con las infecciones de piel y tejidos blandos (IPPB) causadas por microorganismos grampositivos en adultos que recibieron tratamiento antimicrobiano domiciliario endovenoso (TADE), administrado en unidades de hospitalización a domicilio (HaD) en España.

Material y métodos. Estudio observacional, multicéntrico, retrospectivo. Se incluyeron pacientes adultos de ambos sexos, incluidos en el Registro TADE en el periodo 2011 a 2017 y cuyo motivo de ingreso fue una IPPB causada por un microorganismo Grampositivo. El uso de recursos incluyó las visitas a domicilio (enfermería y médico), visitas a urgencias, estancia en hospitalización convencional, estancia en HaD y tratamiento antibiótico. Los costes se cuantificaron multiplicando las unidades naturales de los recursos por el coste unitario correspondiente. Todos los costes fueron actualizados a euros de 2019.

Resultados. Se incluyeron 194 episodios (189 pacientes) procedentes de 24 centros españoles. Los diagnósticos principales más frecuentes fueron celulitis (26,8%) e infección por herida quirúrgica (24,2%). El 94% de los episodios resultaron en una mejoría o curación clínica al finalizar el tratamiento. La mediana de la estancia en HaD fue de 13 días (rango intercuar-

tílico [RI]:8-22,7), con una estancia previa en hospitalización convencional de 5 días (RI: 1-10,7). El coste total promedio atribuible al proceso infecciosos completo fue de 7.326€ (intervalo de confianza del 95%: 6.316€-8.416€).

Conclusiones. Este estudio sugiere que el TADE administrado en HaD es una alternativa segura y eficiente para el manejo de estas infecciones y podría conducir a menores costes en comparación con el ingreso hospitalario.

Palabras clave: TADE, análisis de costes, infecciones de piel y tejidos blandos

INTRODUCTION

Bacterial skin and skin structure infections (BSSSI) encompass infections that affect the skin, skin appendages, subcutaneous cell tissue, fascia, and skeletal muscle [1]. Patients with complicated BSSSI may present with cellulitis/erysipelas (characterized by redness, edema, and/or induration that spreads), wound infections (including surgical site infections), and major skin abscesses [2].

In Spain, skin and skin structure infections (SSSIs) are the fourth most frequent nosocomial infections, according to the EPINE report (Sociedad Española de Medicina Preventiva Salud Pública e Higiene, 2019) and are a frequent reason for consultation in outpatient and hospital settings [3]. The prevalence of SSSIs was found to be 1.6% in Spain, representing 11% (1250 cases) of all emergency service consultations for infection [4].

Although the etiology of SSSIs may include viruses, parasites, bacteria, and fungi some of them as part of the saprophytic flora of the skin and mucous membranes, infections by bacteria are the most frequent, especially those due to Gram-positive bacteria. The most prevalent microorganism is *Staphylococcus aureus,* and its treatment has been complicated by the increase in methicillin-resistant strains [5].

A European study found that antimicrobial treatment did not achieve a clinical cure in 46.6% of complicated SSSIs episodes [6], which may lead to increased mortality in cases of severe sepsis and septic shock in addition [7] to a greater economic cost [8]. Antimicrobial treatment of SSSIs is conditioned by the microorganisms that colonize the skin of the affected area, the acquisition site of the infection, the clinical presentation, risk factors, prior administration of antibiotics, and the local epidemiology of microbial resistance [9].

Hospital at Home (HaH) is an alternative to hospitalization for some patients, which provides levels of care similar to those provided by hospitals [10]. HaH may include outpatient parenteral antimicrobial treatment (OPAT), which consists of the treatment of infectious disease at home, including parenteral administration of the antimicrobial and clinical and analytical controls that indicate the disease evolution [11]. OPAT programs have proven to be an effective and safe alternative to hospitalisation in the treatment of complex infections [12]. HaH has been increasingly used in Spain in recent years [13–15].

The objective of this study was to describe and quantify resource use and direct health costs associated with SSSIs caused by Gram-positive microorganisms in adults receiving OPAT administered in HaH units in Spain.

METHODS

Study design and population. An observational, multicenter, retrospective pharmacoeconomic evaluation was conducted. The study data come from the HaH-based OPAT Registry, a database with hospital records of patients receiving parenteral treatment at home from the HaH unit of the participating centers [16]. The study was classified by the Spanish Agency for Medicines and Health Products (AEMPS) as a Post-Authorisation – Other Designs (EPA-OD) and was approved by the Research Ethics Committee of the Alcorcón Foundation University Hospital.

The study was carried out by analyzing hospitalizations attended by HaH units of the participating centers of the HaH-based OPAT Registry between 2011 and 2017. The economic evaluation was carried out from the perspective of the Spanish National Health System (NHS).

The study focused on resource use and costs associated with episodes of SSSIs caused by Gram-positive bacteria. The records of patients treated with OPAT in each center were used to describe resource use per episode, understanding an episode as the complete infectious process (from conventional hospitalization – if it occurred – to HaH).

The study population included patients aged ≥ 18 years of both sexes included in the HaH-based OPAT Registry and hospitalized due to SSSIs caused by a Gram-positive bacteria. Therefore, the study population was composed of patients who met the general criteria for inclusion in a HaH Unit and the specific criteria for OPAT (Supplementary Table A1).

Data collection. The HaH-based OPAT Registry includes sociodemographic variables (age and sex), clinical variables (Charlson index, main diagnosis, microorganism) and specific OPAT variables (active ingredient, dosage, treatment duration, clinical response, destination at discharge and readmission within 30 days). Diagnoses were recorded using the coding of the Spanish version of the Clinical Modification of the International Classification of Diseases, ninth revision (ICD-9-MC).

Resource use related to SSSIs included home visits (medical and nursing), emergency room visits, conventional hospitalization stay, HaH stay and antimicrobial treatment.

The analysis was based on complete infectious episodes, lasting from the initiation of conventional hospitalization, if any, to HaH discharge, including possible rehospitalization related to the infectious process (Figure 1).

Costs. To estimate the economic impact of SSSIs from the NHS perspective in Spain, direct health costs were included. The unit costs of resource use were obtained from the ESALUD database [17] and pharmacological treatments on the website of the General Council of the Official Colleges of Pharmacists (Bot PLUS) (General Council of Official Colleges of Pharmacists, 2013). The unit cost of the conventional hospital stay was ob-

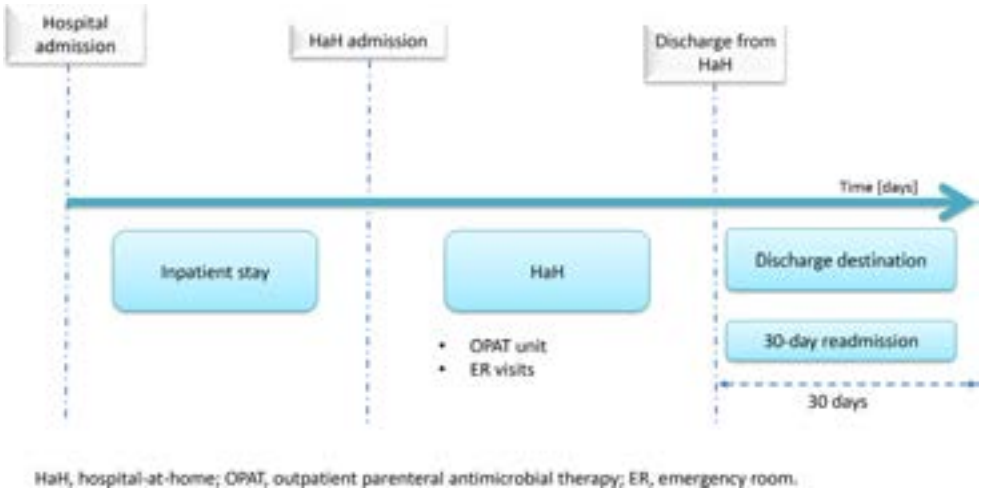

Figure 1 | **Depiction of the complete infectious episodes, covering the time from inpatient hospitalisation, if any, until HaH discharge, including possible returns to the hospital related to the infectious process.**

tained from the CMBD (Ministry of Health, 2019) and the HaH stay was obtained from the literature [13]. All costs were updated to 2019 euros (Supplementary Table A2).

Direct health costs included resource use during hospitalization (conventional and home) due to SSSIs due to Gram-positive bacteria (conventional hospitalization stay, if any, HaH stay, home visits [physician and nurse] and emergency room visits). In episodes in which the patient's discharge destination was related return to the hospital of origin due to SSSIs, the cost per mean stay of conventional hospitalization was added according to the mean hospital stay in Spain.

The costs of visits were calculated by multiplying the number of visits by the unit cost of each visit. The cost of the hospital stay (conventional and home) was obtained by multiplying the days of stay by the corresponding unit cost. The total dose was calculated for each active substance during hospitalization (conventional and home). For this, the dose scheduled for the time on treatment was multiplied. The cost of each pharmacological treatment was obtained by multiplying the total dose that each patient received during hospitalization by the unit cost of each treatment. The wholesale price was applied without VAT, according to the presentation of the medicine.

If HaH discharge was followed by readmission within 30 days, the readmission cost was added to the original cost of the episode. The readmission may have been in the home OPAT service or in conventional hospitalization. If readmission was in the OPAT service, all data necessary to calculate the cost of re-entry using the previous methodology was available in the HaH-based OPAT Registry. If readmission within 30 days was in conventional hospitalization, the HaH-based OPAT Registry does not have the information corresponding to the associated resource use and the cost was estimated according to the cost per mean hospital stay in Spain.

Stratification. Stratification analyses were made to estimate the hospital stay and the cost of SSSIs according to the main diagnosis (cellulitis, surgical wound infection, diabetic foot infection, skin abscess, vascular ulcer infection, pressure ulcer infection, traumatic wound infection and other SSSIs).

Statistical analysis. All analyses were performed using complete infectious episodes as the unit of analysis. A descriptive analysis of the variables included in the study was made. Quantitative variables were described using means, standard deviation (SD), medians and interquartile range (IQR). Qualitative variables were analyzed using absolute and relative frequencies. For cost variables, the mean and 95% confidence intervals (CI) were used. The CIs were obtained using the bootstrapping technique, given the non-normality of the results. The R (version 3.6.1) statistical package was used for the statistical analysis.

RESULTS

The initial cohort included 1,055 patients (1,160 episodes) with SSSIs from the 24 participating centers: 189 patients (194 episodes) met the criteria for analysis (Figure 2).

Most patients were male (54.6%) with a median age of 63 years (IQR: 53.7–77.5). In approximately 40% of episodes, patients had high comorbidity with a Charlson index ≥3 points. The most frequent main diagnoses were cellulitis (26.8%) and surgical wound infection (24.2%), while the most frequent causal microorganism was *Staphylococcus aureus* (57.7%) (Table 1).

The clinical results are shown in table 1. In > 90% of episodes, there was an improvement or cure of the infection after OPAT. The discharge destination from HaH was the home/nurs-

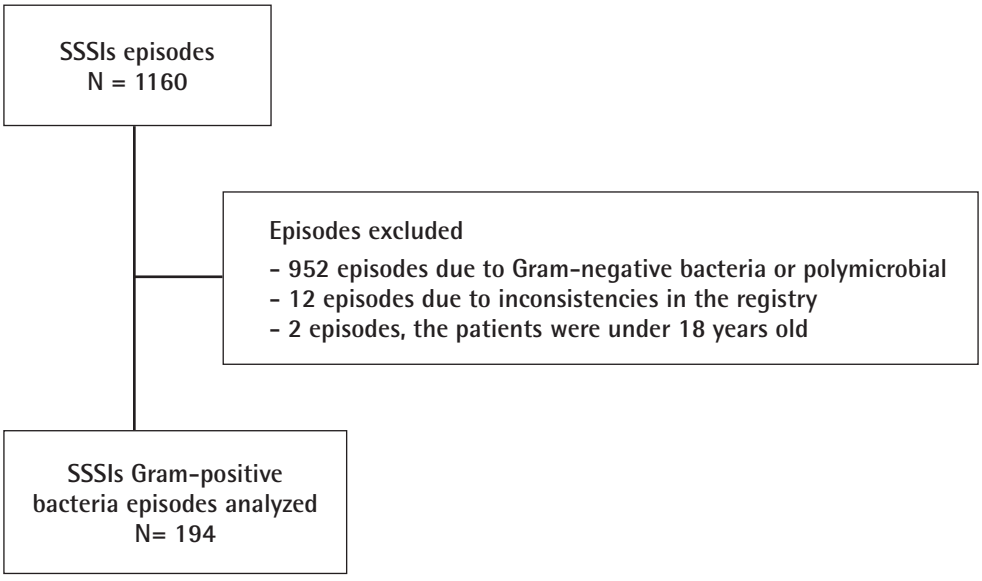

Figure 2 Flowchart of the episodes included in the analysis

SSSIs, skin and skin structure infections.

ing home/social health center of origin in 91.2% of episodes while, in 14 episodes related return to the hospital of origin was required (10 episodes of SSSIs due to Gram-positive bacteria and 4 episodes due to other causes). There were 6.2% of readmissions for any cause during the 30 days following discharge. In 92.0% of these, the entire stay due to readmission was in conventional hospitalization and the rest were treated in HaH (Table 1).

Resource use. The mean duration (SD) of admission for the complete infectious process was 26.1 days (20.9), of which 8.0 (10.6) days corresponded to the mean conventional hospitalization stay and 18.1 (16.7) days to the HaH stay. The median HaH stay was 13 days [IQR: 8.0-22.7] (Table 2). The most frequently used antibiotics were daptomycin (28.3%), ertapenem (19.1%) and ceftriaxone (15.5%) (Table 2).

The mean rate (SD) of home visits by the HaH unit team was 1.2 (0.32) visits per day of home stay. A nurse attended almost daily during admission to the HaH unit (0.86 visits per day of stay) while medical visits occurred approximately every three days (0.37 visits per day of stay). Visits to the emergency room were uncommon, with a mean rate of 1 (3.3) visits per 100 days of HaH (Table 2).

Costs. Table 3 shows the costs of the complete infectious process, including conventional hospitalization if any, HaH unit admission, return to the hospital related to the infectious process and rehospitalization for any cause during the 30 days after discharge. During the study period, the mean cost per episode of the complete infectious process was €7,326 (95% CI: 6,316–8,416), of which the cost of admission to HaH was €1,528 (95% CI: 1,353–1,734), representing 21% of the cost.

Days of stay and costs according to the main diagnosis. Figure 3 shows the length of stay (Figure 3a) and the total costs (Figure 3b) of the complete infectious process according to the main diagnosis that motivated hospital admission. The main diagnosis due to surgical wound infection had a longer median stay (28 days [IQR: 17.0–40.5]) and a higher mean cost (€12,438 [95% CI: 9,686–15,525]), compared with the other main diagnoses. These results should be interpreted with caution due to the small sample size in the subgroups.

DISCUSSION

In this study, the cost of the conventional hospital stay before home hospital admission was included, so the cost of the complete infectious process (conventional and home) of SSSIs due to Gram-positive bacteria requiring hospital admission was estimated. A notable difference was observed in the total cost of conventional hospitalization and that of HaH. In times of financial constraints, OPAT has advantages in the treatment of SSSIs requiring intravenous treatment and clinical follow-up.

SSSIs are a significant economic burden for the Spanish NHS due to hospital treatments, surgical procedures and pharmacological treatment. In general, patients with SSSIs are difficult to treat, and those with comorbidities have longer hospital stays, a higher rate of modification of the initial antimicrobial treatment, greater reinfection or recurrence, and higher mortality rates, compared with patients with SSSIs

Table 1 **Baseline characteristics and efficacy results of OPAT in patients with SSSIs due to Gram-positive bacteria**

VARIABLE Baseline characteristics	
Age [years][a]	
Median [IQR]	63.2 [53.7;77.5]
Sex - n (%)	
Male	106 (54.6%)
Charlson index - n (%)[b]	
<3 points	102 (60.4%)
≥3 points	67 (39.6%)
Median [IQR]	2.0 [1.0;3.0]
Main diagnosis - n (%)	
Cellulitis	52 (26.8%)
Surgical wound infection	47 (24.2%)
Diabetic foot infection	23 (11.9%)
Skin abscess	21 (10.8%)
Other skin and skin structure Infections	21 (10.8%)
Vascular ulcer infection	14 (7.2%)
Pressure ulcer infection	13 (6.7%)
Traumatic wound infection	3 (1.5%)
Microorganism - n (%)[c]	
Staphylococcus aureus	112 (57.7%)
Streptococcus agalactiae	14 (7.2%)
Staphylococcus epidermidis	13 (6.7%)
Enterococcus faecalis	11 (5.7%)
Staphylococcus (coagulase negative) other spp	9 (4.6%)
Streptococcus pyogenes	9 (4.6%)
Streptococcus group viridians	8 (4.1%)
Staphylococcus lugdunensis	6 (3.1%)
Streptococcus other spp	6 (3.1%)
Other	15 (7.7%)

VARIABLE Baseline characteristics	
Referring service[d]	
Medical	73 (37.6%)
Surgical	68 (35.1%)
Emergency	35 (18.0%)
Other service	16 (8.2%)
Not available service	2 (1.0%)
OPAT efficacy results	
Clinical response - n (%)[e]	
Improvement	103 (56.0%)
Healing	70 (38.0%)
Failure	6 (3.3%)
Relapse	2 (1.1%)
Other	3 (1.6%)
Discharge destination - n (%)	
Home	171 (88.1%)
SSSIs-related return	10 (5.1%)
Residence/social health center	6 (3.1%)
Return unrelated to SSSIs	4 (2.1%)
Death	2 (1.0%)
Another hospital	1 (0.5%)
Readmission within 30 days – n (%)	12 (6.2%)

Valid N = 194 episodes with SSSIs due to Gram-positive bacteria. SSSIs, skin and skin structure infections; OPAT, oral parenteral antibiotic therapy; IQR, interquartile range. [a]Age at admission to hospital at home. [b]Information available in 169 episodes. [c]Other microorganisms: *Clostridium* other spp, *Corynebacterium* spp, *Enterococcus faecium*, *Enterococcus* other spp, *Finegoldia magna*, *Peptostreptococcus anaerobius*, *Propionibacterium* spp, *Staphylococcus haemolyticus*, *Staphylococcus homonis*, *Streptococcus pneumoniae*. [d]Surgical service: Angiology and vascular surgery, cardiovascular surgery, general and digestive system surgery, plastic and reconstructive surgery, gynecology and obstetrics, traumatology and orthopedics and urology. Medical service: Cardiology, infectious diseases, internal medicine, nephrology, pulmonology, medical oncology, rheumatology. [e]Information available in 184 episodes.

without comorbidities [20,21]. In this analysis, we found that 40% of HaH patients had a Charlson comorbidity index score of ≥3 points. Several studies have analyzed the economic impact in Spain of patients with SSSIs. The mean cost per patient treated varies between €2,857 and €7,917 [22–25], meaning an annual expenditure of between €13.5 and €23.5 million [26,27].

Our results show that the mean cost per complete infectious episode was € 7,326, of which 71.6% (€ 5,246) was due to conventional hospitalization and 20.8% (€ 1,528) to HaH. The mean cost obtained is higher than that found in other studies. A possible explanation is that our analysis includes the resources used throughout the infectious process (including readmissions from HaH due to poor evolution and readmissions 30 days after HaH discharge) in real clinical practice. Various studies have found HaH units are a good option for the management and control of serious and complex infections [13,14,28]. The costs of OPAT have been calculated in several studies [29–38]. All concluded that OPAT is equally as safe and effective as conventional hospitalization at a lower cost. This suggests that OPAT for serious and complex infections may be an alternative in which HaH units are more efficient, reducing the stay and avoiding hospital admission [39].

We found the overall mean stay (conventional hospitalization and OPAT) was 26.1 days, slightly higher than the 18.5 days observed in an observational study in 10 European countries in patients hospitalized due to complicated SSSIs (Ostermann et al., 2014). One reason for the increased stay may be that, in our series, 24% of patients had surgical wound infection, compared with 12% of those in the RECH study [21], which implies a longer hospital stay due to the

Table 2 Resource use per episode associated with SSSIs due to Gram-positive bacteria

VARIABLE	
Hospital stay	**Mean (SD)** **Median [IQR]**
Number of days of the episode of SSSIs due to Gram-positive bacteria	26.1 (20.9) 19.0 [12.0;34.7]
Number of days of previous conventional hospitalization	8.0 (10.6) 5.0 [1.0;10.7]
Days without antimicrobial treatment	4.5 (9.1) 0.0 [0.0;5.0]
Days with antimicrobial treatment	3.5 (6.0) 1.0 [0.0;5.0]
Number of days in HaH	18.1 (16.7) 13.0 [8.0;22.7]
Days without antimicrobial treatment	6.4 (13.4) 1.0 [0.0;7.0]
Days with antimicrobial treatment	11.7 (9.7) 8.0 [6.0;14.0]
Number of visits	**Mean (SD)**
Rate of total visits (physicians + nursing)	1.23 (0.32)
Rate of medical visits	0.37 (0.14)
Rate of nursing visits	0.86 (0.24)
Rate of emergency visits[a]	1 (3.3)
Antibiotic treatments	**n (%)**
Daptomycin	55 (28.3%)
Ertapenem	37 (19.1%)
Ceftriaxone	30 (15.5%)
Piperacillin - tazobactam	21 (10.8%)
Cloxacillin	19 (9.8%)
Vancomycin	17 (8.8%)
Teicoplanin	9 (4.6%)
Levofloxacin	7 (3.6%)
Meropenemb	7 (3.6%)
Amoxicillin - clavulanic[b]	6 (3.1%)
Gentamicin	5 (2.6%)
Linezolid	4 (2.1%)
Clindamycin	2 (1.0%)
Imipenem - cilastatin[b]	2 (1.0%)
Penicillin G sodium	2 (1.0%)
Other[c]	6 (3.1%))

Valid N = 194 episodes of gram-positive SSSIs. SSSIs, skin and skin structure infections; CH conventional hospitalization; HaH, hospital at home; OPAT, oral parenteral antibiotic therapy; SD, standard deviation; IQR, interquartile range.

[a]Visitation rate per 100 days of HaH stay.

[b]Self-administered intravenous antibiotics.

[c]Others: amikacin, ampicillin, cefazolin, ceftazidime, ciprofloxacin and tigecycline.

study of post-surgical fever, the need for drainage, reoperations, etc. Some studies have found that episodes of patients undergoing OPAT have a longer stay compared with conventional hospitalization. For example, a mean duration of 24 days of OPAT was observed in a cohort of 72 patients, which lasted up to 42 days when the duration of previous hospital treatment was added, a far cry from the 19 days of treatment in comparison groups of hospitalized patients [32].

Table 3 Cost (euros) per episode associated with SSSIs due to Gram-positive bacteria

VARIABLE	Mean (95% CI)
Cost of previous conventional hospitalization - Total	5,246 (4,332 - 6,295)
Cost of conventional hospitalization	5,137 (4,230 - 6,168)
Cost of antimicrobial treatment	109 (78.4 - 148)
HaH Cost - Total	1,528 (1,353 - 1,734)
Cost of HaH stay	1,085 (956 - 1,239)
Cost of antimicrobial treatment	443 (365 - 532)
Cost of discharge destination	274 (124 - 423)
Cost of 30-day readmission	278 (133 - 452)
Total cost	7,326 (6,316 - 8,416)

Valid N = 194 episodes of gram-positive SSSIs.
SSSIs, skin and skin structure infections; HaH, hospital at home; CI, confidence intervals.

This may indicate that patients may be selected for OPAT because they have infections requiring longer antimicrobial treatments. These patients also often have infections due to multidrug-resistant pathogens with no alternative oral antibiotic use, which means all treatment must be with parenteral antibiotics. Almost half of the patients in our study had secondary infections (surgical wound infection, diabetic foot infections, pressure ulcer infection, vascular ulcers), which may have contributed to the longer length of stay. In these cases, it is more difficult to reach the antibiotic concentration in the focus, which is essential for eradicating microorganisms. In addition, the characteristics inherent in the HaH model, such as the time spent travelling, which limits the number of times the patient is seen, may contribute to a longer total stay. However, this does not translate into higher costs or worse care.

We found a rate of cure or improvement of > 90%, similar to the findings of other studies (87%-92%) [31,40,41]. Theocharis et al. [35] found a significantly lower cure rate (72.5%), although the patients treated were older (mean of 85 years vs 64 years in our cohort) and the associated mortality rate was 27.5%, much higher than the 1% found in our study. The quality of care of the OPAT program in HaH units is reflected in the rate of readmissions in 30 days (6.2%), similar to that found in other studies, as shown by the review by Chapman et al. [42] .

Studies have found that the inadequate use of antimicrobials, including inappropriate choices or administration, is associated with the expansion of multidrug-resistant strains [43,44]. The complex management of infectious diseases and the increase in resistance has led to the introduction of antimicrobial use optimization programs (PROA) in hospitals [45,46], which have been shown to improve the prognosis by optimizing the prescription of antibiotics. Therefore, the use of effective, safe, easy-to-use antibiotics for the treatment of Gram-positive bacterial infections is of special clinical relevance, as it has been observed that, for example, vancomycin, teicoplanin, daptomycin and linezolid have limitations due to toxicity, tolerance and drug resistance [47–53]. Inappropriate antibiotic use is also associated with increased costs due to prolongation of the hospital stay, so the cost of the drug should not be used as the only criterion for the selection of treatment.

Novel antibiotics effective against multidrug-resistant Gram-positive bacteria have been approved in recent years, such as tedizolid (oxazolidinone oral or intravenous administration) [54], delafloxacin (4th generation quinolone oral or intravenous administration) [55], dalbavancin [56] and oritavancin [57] which can facilitate the outpatient treatment of BSSSI. Due to their long half-lives, dalbavancin (two-dose) and oritavancin (single-dose) have promising potential to reduce the number of hospital stays and for use within the OPAT program in HaH units, particularly in vulnerable patients and/or those with low adherence [58,59]. The possibility of reducing the number of visits can offset the higher cost of these antibiotics.

LIMITATIONS

The study has some limitations which may have influenced the results. Firstly, the retrospective nature: however, it was not possible to compare costs using a prospective study in which patients were randomly assigned to one of two treatment groups, hospital or home. However, our study shows the strength of an analysis in real clinical practice. Second, the unit cost considered for the day of HaH stay. Due to the study design, we could not estimate the costs based on the accounts of the hospitals, so this was extracted from the literature. In any case, the unit cost assumed comes from an estimate made in the HaH-based OPAT Registry [13] from the analytical accounting of the participating hospitals, so we consider that the estimate is adjusted to reality. Although the total costs were representative of episodes of SSSIs caused by Gram-positive bacteria in each center, they may not be representative of the episodes in centers not participating in the HaH-based OPAT Registry or of global episodes of SSSIs in Spain.

CONCLUSIONS

SSSIs caused by Gram-positive bacteria result in a significant consumption of resources and costs by the Spanish NHS, and the conventional hospitalization stay is the main contributor. Our results suggest that OPAT administered by HaH is a safe, efficient alternative for the management of these infections and could lead to lower costs compared with hospital admission.

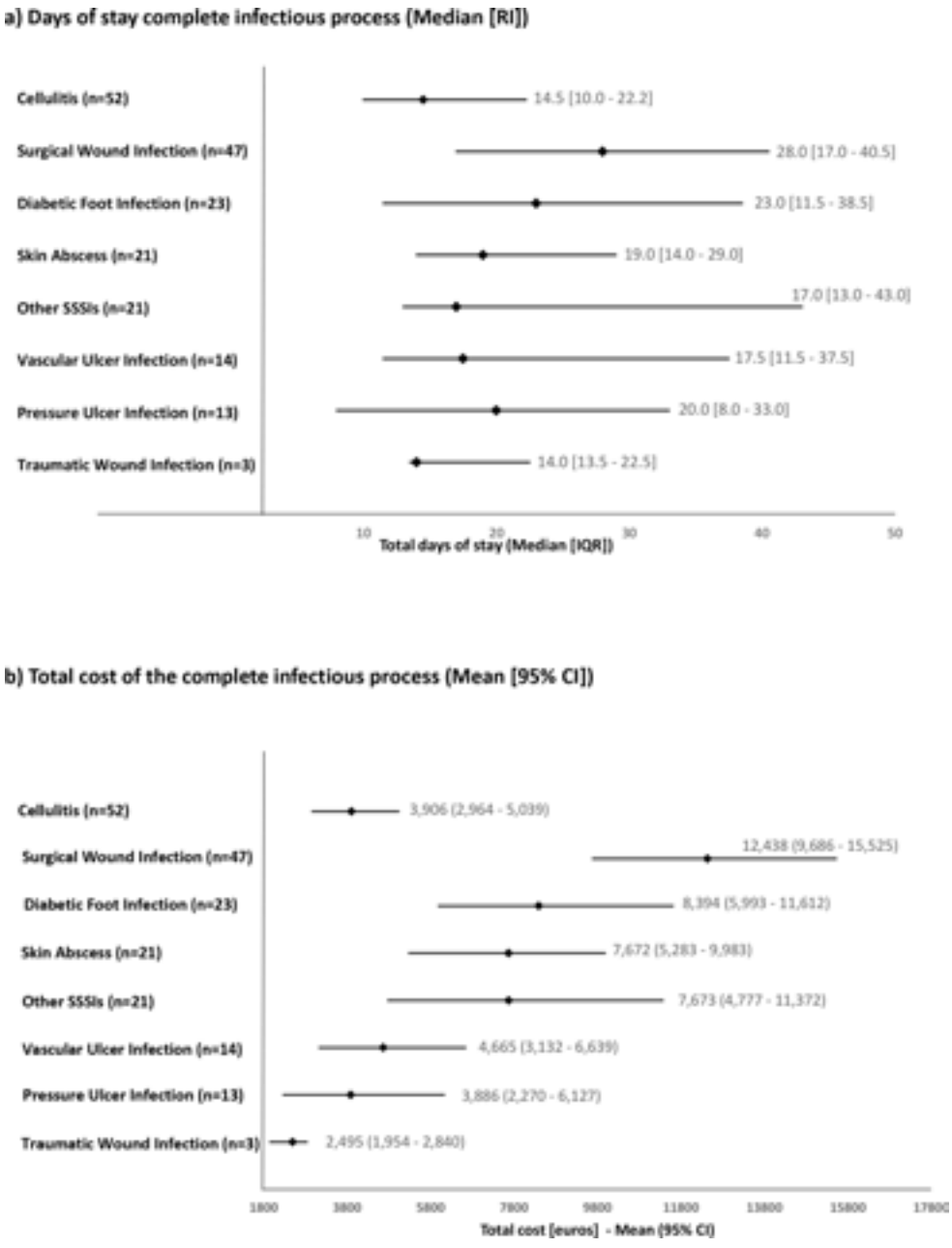

Figure 3 | **Hospital stay and total cost associated with episodes of SSSIs due to Gram-positive bacteria according to main diagnosis**

SSSIs, skin and skin structure infections; IR, interquartile range; CI, confidence interval.

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Manuel Mirón Rubio received fees as a speaker in conferences from Merck Sharp and Dohme, Aldo-Unión Lab, and has lectured at meetings organized by pharmaceutical companies (Merck Share and Dohme, Rovi, Angelini Pharma) or participated in some medical advice.

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REFERENCES

1 Conde García M del C, Patiño Ortega HD. Protocolo de infecciones bacterianas agudas de la piel y partes blandas. SESCAM 2016.

2 Russo A, Concia E, Cristini F, De Rosa FG, Esposito S, Menichetti F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. Clin Microbiol Infect 2016;22 Suppl 2:S27-36. https://doi.org/10.1016/S1198-743X(16)30095-7.

3 Raya-Cruz M, Ferullo I, Arrizabalaga-Asenjo M, Nadal-Nadal A, Díaz-Antolín MP, Garau-Colom M, et al. [Skin and soft-tissue infections in hospitalized patients: epidemiology, microbiological, clinical and prognostic factors]. Enferm Infecc Microbiol Clin 2014;32:152–9. https://doi.org/10.1016/j.eimc.2013.03.004.

4 Llopis F, González-Castillo J, Julián-Jiménez A, Ferré C, Gamazo-Río JJ, Martínez M, et al. [Review of 1.250 episodes of skin and soft tissue infections attended at 49 hospital emergency departments]. Rev Esp Quimioter 2014;27:115–21.

5 Pulido-Cejudo A, Guzmán-Gutierrez M, Jalife-Montaño A, Ortiz-Covarrubias A, Martínez-Ordaz JL, Noyola-Villalobos HF, et al. Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. Ther Adv Infect Dis 2017;4:143–61. https://doi.org/10.1177/2049936117723228.

6 Bassetti M, Baguneid M, Bouza E, Dryden M, Nathwani D, Wilcox M. European perspective and update on the management of complicated skin and soft tissue infections due to methicillin-resistant Staphylococcus aureus after more than 10 years of experience with linezolid. Clin Microbiol Infect 2014;20 Suppl 4:3–18. https://doi.org/10.1111/1469-0691.12463.

7 González Del Castillo J, Sánchez-Marcos C, Nuñez-Orantos MJ, Martín-Sánchez FJ. Treatment Adequacy of Antibiotics in Severe Sepsis. J Emerg Med 2016;51:e63-4. https://doi.org/10.1016/j.jemermed.2015.03.049.

8 Shorr AF. Epidemiology and economic impact of meticillin-resistant Staphylococcus aureus: review and analysis of the literature. Pharmacoeconomics 2007;25:751–68. https://doi.org/10.2165/00019053-200725090-00004.

9 Porras Leal L, Sáenz Gutiérrez A, Calderón Jiménez P, Gijón Rodríguez J. Protocolo de Enfermedades Infecciosas. Capitulo 5 - Infecciones de piel y partes blandas. Sociedad Española de Medicina Interna 2009.

10 Alonso G, Escudero JM. [The emergency department short stay unit and the hospital at home as alternatives to standard inpatient hospitalisation]. An Sist Sanit Navar 2010;33 Suppl 1:97–106.

11 Mirón-Rubio M, Estrada Cuxart O, González Ramallo VJ. Tratamiento antimicrobiano domiciliario endovenoso (TADE). Sociedad Española de Medicina Interna (SEMI) 2008:15.

12 Candel FJ, Julián-Jiménez A, González-Del Castillo J. Current status in outpatient parenteral antimicrobial therapy: a practical view. Rev Esp Quimioter 2016;29:55–68.

13 González-Ramallo VJ, Mirón-Rubio M, Mujal A, Estrada O, Forné C, Aragón B, et al. Costs of outpatient parenteral antimicrobial therapy (OPAT) administered by Hospital at Home units in Spain. Int J Antimicrob Agents 2017;50:114–8. https://doi.org/10.1016/j.ijantimicag.2017.02.017.

14 González-Ramallo VJ, Mirón Rubio M, Estrada Cuxart O, García Leoni ME. Usefulness of Hospital at Home in nosocomial infections: advantages and limitations. Rev Esp Quimioter 2017;30 Suppl 1:61–5.

15 Mujal A, Sola J, Hernandez M, Villarino M-A, Machado M-L, Baylina M, et al. Safety and effectiveness of home intravenous antibiotic therapy for multidrug-resistant bacterial infections. Eur J Clin Microbiol Infect Dis 2015;34:1125–33. https://doi.org/10.1007/s10096-015-2330-0.

16 Mirón-Rubio M, González-Ramallo V, Estrada-Cuxart O, Sanroma-Mendizábal P, Segado-Soriano A, Mujal-Martínez A, et al. Intravenous antimicrobial therapy in the hospital-at-home setting: data from the Spanish Outpatient Parenteral Antimicrobial Therapy Registry. Future Microbiol 2016;11:375–90. https://doi.org/10.2217/fmb.15.141.

17 Gisbert R, Brosa M. Healthcare cost database eSALUD. Oblikue Consulting, SL 2015. http://www.oblikue.com/en/index.htm (accessed December 15, 2022).

18 Consejo General de Colegios Oficiales de Farmacéuticos. Bot PLUS 2.0 2013. https://botplusweb.portalfarma.com (accessed July 1, 2019).

19 Ministerio de Sanidad C y BS. Registro de Actividad de Atención Especializada - RAE-CMBD 2019. http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/comun/DefaultPublico.aspx (accessed July 1, 2019).

20 Garau J, Ostermann H, Medina J, Avila M, McBride K, Blasi F, et al. Current management of patients hospitalized with complicated skin and soft tissue infections across Europe (2010-2011): assessment of clinical practice patterns and real-life effectiveness of antibiotics from the REACH study. Clin Microbiol Infect 2013;19:E377-85. https://doi.org/10.1111/1469-0691.12235.

21 Ostermann H, Blasi F, Medina J, Pascual E, McBride K, Garau J, et al. Resource use in patients hospitalized with complicated skin and soft tissue infections in Europe and analysis of vulnerable groups: the REACH study. J Med Econ 2014;17:719–29. https://doi.org/10.3111/13696998.2014.940423.

22 González García J, Madueño Alonso A, Gutiérrez Nicolás F, Nazco Casariego G, Valcárcel Nazco C, González de la Fuente G, et al. Análisis farmacoeconómico de las infecciones complicadas de

la piel y partes blandas con ceftarolina o la combinación de vancomicina y aztreonam en España. Rev OFIL 2017;27:193–9.

23 Arrieta-Loitegui M, Caro-Teller JM, Ortiz-Pérez S, López-Medrano F, San Juan-Garrido R, Ferrari-Piquero JM. Effectiveness, safety and cost analysis of dalbavancin in clinical practice. Eur J Hosp Pharm 2020. https://doi.org/10.1136/ejhpharm-2020-002315.

24 Soriano A, Grau S, Rivolo S, Remak E, Peral C, Kantecki M, et al. PIN63 - A COST-MINIMIZATION MODEL TO EVALUATE THE IMPACT OF CEFTAROLINE FOSAMIL FOR THE TREATMENT OF COMPLICATED SKIN AND SOFT TISSUE INFECTIONS IN HOSPITALIZED ADULTS IN SPAIN. Value in Health 2018;21:S231. https://doi.org/10.1016/j.jval.2018.09.1382.

25 Bouza E, Valerio M, Soriano A, Morata L, Carus EG, Rodríguez-González C, et al. Dalbavancin in the treatment of different gram-positive infections: a real-life experience. Int J Antimicrob Agents 2018;51:571–7. https://doi.org/10.1016/j.ijantimicag.2017.11.008.

26 Marcellusi A, Bini C, Andreoni M, Sarmati L, Espin J, Horcajada JP, et al. Budget Impact Analysis of Dalbavancin in the Treatment of Acute Bacterial Skin and Skin Structure Infections in Three European Countries. Clin Drug Investig 2020;40:305–18. https://doi.org/10.1007/s40261-020-00891-w.

27 Marcellusi A, Viti R, Sciattella P, Sarmati L, Streinu-Cercel A, Pana A, et al. Economic evaluation of the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) from the national payer perspective: introduction of a new treatment to the patient journey. A simulation of three European countries. Expert Rev Pharmacoecon Outcomes Res 2019;19:581–99. https://doi.org/10.1080/14737167.2019.1569516.

28 García-Queiruga M, Feal Cortizas B, Lamelo Alfonsín F, Pertega Diaz S, Martín-Herranz I. Continuous infusion of antibiotics using elastomeric pumps in the hospital at home setting. Rev Esp Quimioter 2021;34:200–6. https://doi.org/10.37201/req/122.2020.

29 Wolter JM, Cagney RA, McCormack JG. A randomized trial of home vs hospital intravenous antibiotic therapy in adults with infectious diseases. J Infect 2004;48:263–8. https://doi.org/10.1016/S0163-4453(03)00135-X.

30 Fisher DA, Kurup A, Lye D, Tambyah PA, Sulaiman Z, Poon EYH, et al. Outpatient parenteral antibiotic therapy in Singapore. Int J Antimicrob Agents 2006;28:545–50. https://doi.org/10.1016/j.ijantimicag.2006.08.018.

31 Chapman ALN, Dixon S, Andrews D, Lillie PJ, Bazaz R, Patchett JD. Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): a UK perspective. J Antimicrob Chemother 2009;64:1316–24. https://doi.org/10.1093/jac/dkp343.

32 Yong C, Fisher DA, Sklar GE, Li S-C. A cost analysis of Outpatient Parenteral Antibiotic Therapy (OPAT): an Asian perspective. Int J Antimicrob Agents 2009;33:46–51. https://doi.org/10.1016/j.ijantimicag.2008.07.016.

33 Baharoon S, Almodaimeg H, Al Watban H, Al Jahdali H, Alenazi T, Al Sayyari A, et al. Home intravenous antibiotics in a tertiary care hospital in Saudi Arabia. Ann Saudi Med 2011;31:457–61. https://doi.org/10.4103/0256-4947.84621.

34 Gray A, Dryden M, Charos A. Antibiotic management and early discharge from hospital: an economic analysis. J Antimicrob Chemother 2012;67:2297–302. https://doi.org/10.1093/jac/dks194.

35 Theocharis G, Rafailidis PI, Rodis D, Kontopidis I, Barbas SG, Falagas ME. Outpatient parenteral antibiotic therapy (OPAT) at home in Attica, Greece. Eur J Clin Microbiol Infect Dis 2012;31:2957–61. https://doi.org/10.1007/s10096-012-1647-1.

36 Seaton RA, Johal S, Coia JE, Reid N, Cooper S, Jones BL. Economic evaluation of treatment for MRSA complicated skin and soft tissue infections in Glasgow hospitals. Eur J Clin Microbiol Infect Dis 2014;33:305–11. https://doi.org/10.1007/s10096-013-1956-z.

37 Czoski Murray C, Twiddy M, Meads D, Hess S, Wright J, Mitchell ED, et al. Community IntraVenous Antibiotic Study (CIVAS): protocol for an evaluation of patient preferences for and cost-effectiveness of community intravenous antibiotic services. BMJ Open 2015;5:e008965. https://doi.org/10.1136/bmjopen-2015-008965.

38 Ruh CA, Parameswaran GI, Wojciechowski AL, Mergenhagen KA. Outcomes and Pharmacoeconomic Analysis of a Home Intravenous Antibiotic Infusion Program in Veterans. Clin Ther 2015;37:2527–35. https://doi.org/10.1016/j.clinthera.2015.09.009.

39 Shepperd S, Doll H, Angus RM, Clarke MJ, Iliffe S, Kalra L, et al. Avoiding hospital admission through provision of hospital care at home: a systematic review and meta-analysis of individual patient data. CMAJ 2009;180:175–82. https://doi.org/10.1503/cmaj.081491.

40 Partridge DG, O'Brien E, Chapman ALN. Outpatient parenteral antibiotic therapy for infective endocarditis: a review of 4 years' experience at a UK centre. Postgrad Med J 2012;88:377–81. https://doi.org/10.1136/postgradmedj-2011-130355.

41 Barr DA, Semple L, Seaton RA. Outpatient parenteral antimicrobial therapy (OPAT) in a teaching hospital-based practice: a retrospective cohort study describing experience and evolution over 10 years. Int J Antimicrob Agents 2012;39:407–13. https://doi.org/10.1016/j.ijantimicag.2012.01.016.

42 Chapman ALN, Seaton RA, Cooper MA, Hedderwick S, Goodall V, Reed C, et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. J Antimicrob Chemother 2012;67:1053–62. https://doi.org/10.1093/jac/dks003.

43 De Angelis G, Restuccia G, Cauda R, Tacconelli E. How could we reduce antibiotic use in critically ill patients? Infect Disord Drug Targets 2011;11:376–83. https://doi.org/10.2174/187152611796504791.

44 Bryce A, Hay AD, Lane IF, Thornton H V, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 2016:i939. https://doi.org/10.1136/bmj.i939.

45 Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, Asensio Á, Calbo E, Cercenado E, et al. [Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document]. Farm Hosp 2012;36:33.e1-30. https://doi.org/10.1016/j.farma.2011.10.001.

46 Ruiz J, Salavert M, Ramírez P, Montero M, Castro I, González E, et al. [Antimicrobial stewardship programme implementation in a medical ward]. Rev Esp Quimioter 2018;31:419–26.

47 Lee E, Burger S, Shah J, Melton C, Mullen M, Warren F, et al. Linezolid-associated toxic optic neuropathy: a report of 2 cases. Clin Infect Dis 2003;37:1389–91. https://doi.org/10.1086/379012.

48 Frippiat F, Derue G. Causal relationship between neuropathy and prolonged linezolid use. Clin Infect Dis 2004;39:439. https://doi.org/10.1086/422147.

49 Kim PW, Sorbello AF, Wassel RT, Pham TM, Tonning JM, Nambiar S. Eosinophilic pneumonia in patients treated with daptomycin: review of the literature and US FDA adverse event reporting system reports. Drug Saf 2012;35:447–57. https://doi.org/10.2165/11597460-000000000-00000.

50 Álvarez R, López Cortés LE, Molina J, Cisneros JM, Pachón J. Optimizing the Clinical Use of Vancomycin. Antimicrob Agents Chemother 2016;60:2601–9. https://doi.org/10.1128/AAC.03147-14.

51 Decousser J-W, Desroches M, Bourgeois-Nicolaos N, Potier J, Jehl F, Lina G, et al. Susceptibility trends including emergence of linezolid resistance among coagulase-negative staphylococci and meticillin-resistant Staphylococcus aureus from invasive infections. Int J Antimicrob Agents 2015;46:622–30. https://doi.org/10.1016/j.ijantimicag.2015.07.022.

52 Krull M, Klare I, Ross B, Trenschel R, Beelen DW, Todt D, et al. Emergence of linezolid- and vancomycin-resistant Enterococcus faecium in a department for hematologic stem cell transplantation. Antimicrob Resist Infect Control 2016;5:31. https://doi.org/10.1186/s13756-016-0131-6.

53 Eells SJ, Nguyen M, Jung J, Macias-Gil R, May L, Miller LG. Relationship between Adherence to Oral Antibiotics and Postdischarge Clinical Outcomes among Patients Hospitalized with Staphylococcus aureus Skin Infections. Antimicrob Agents Chemother 2016;60:2941–8. https://doi.org/10.1128/AAC.02626-15.

54 Sahre M, Sabarinath S, Grant M, Seubert C, Deanda C, Prokocimer P, et al. Skin and soft tissue concentrations of tedizolid (formerly torezolid), a novel oxazolidinone, following a single oral dose in healthy volunteers. Int J Antimicrob Agents 2012;40:51–4. https://doi.org/10.1016/j.ijantimicag.2012.03.006.

55 Millar BC, McCaughan J, Rendall JC, Moore JE. Delafloxacin--A novel fluoroquinolone for the treatment of ciprofloxacin-resistant Pseudomonas aeruginosa in patients with cystic fibrosis. Clin Respir J 2021;15:116–20. https://doi.org/10.1111/crj.13262.

56 Dash RP, Babu RJ, Srinivas NR. Review of the pharmacokinetics of dalbavancin, a recently approved lipoglycopeptide antibiotic. Infect Dis (Lond) 2017;49:483–92. https://doi.org/10.1080/23744235.2017.1296968.

57 Saravolatz LD, Stein GE. Oritavancin: A Long-Half-Life Lipoglycopeptide. Clin Infect Dis 2015;61:627–32. https://doi.org/10.1093/cid/civ311.

58 Bork JT, Heil EL, Berry S, Lopes E, Davé R, Gilliam BL, et al. Dalbavancin Use in Vulnerable Patients Receiving Outpatient Parenteral Antibiotic Therapy for Invasive Gram-Positive Infections. Infect Dis Ther 2019;8:171–84. https://doi.org/10.1007/s40121-019-0247-0.

59 Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, et al. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis 2015;60:254–62. https://doi.org/10.1093/cid/ciu778.

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Activity of imipenem/relebactam against Enterobacterales and *Pseudomonas aeruginosa* in Spain. SMART 2016-2020

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ABSTRACT

Objectives. To determine susceptibility to the novel β-lactam/β-lactamase inhibitor combination imipenem/relebactam in clinical isolates recovered from intra-abdominal (IAI), urinary (UTI), respiratory (RTI) and bloodstream (BSI) infections in the SMART (Study for Monitoring Antimicrobial Resistance Trends) study in SPAIN during 2016 – 2020.

Methods. Broth microdilution MICs for imipenem/relebactam and comparators were determined by a central laboratory against isolates of Enterobacterales and *Pseudomonas aeruginosa*. MICs were interpreted using EUCAST-2021 breakpoints.

Results. In total, 5,210 Enterobacterales and 1,418 *P. aeruginosa* clinical isolates were analyzed. Imipenem/relebactam inhibited 98.8% of Enterobacterales. Distinguishing by source of infection susceptibility was 99.1% in BSI, 99.2% in IAI, 97.9% in RTI, and 99.2% in UTI. Of intensive care unit isolates (ICU) 97.4% were susceptible and of non-ICU isolates 99.2% were susceptible. In Enterobacterales, activity against Class A, Class B and Class D carbapenemases was 96.2%, 15.4% and 73.2%, respectively. In *P. aeruginosa*, imipenem/relebactam was active in 92.2% of isolates. By source of infection it was 94.8% in BSI, 92.9% in IAI, 91.7% in RTI, and 93.1% in UTI. An 88.7% of ICU isolates and 93.6% of non-ICU isolates were susceptible to imipenem/relebactam. Imipenem/relebactam remained active against *P. aeruginosa* ceftazidime-resistant (76.3%), cefepime-resistant (73.6%), imipenem-resistant (71.5%) and piperacillin-resistant (78.7%) isolates. Of all multidrug-resistant or difficult-to-treat resistance *P. aeruginosa* isolates, 75.1% and 46.2%, respectively, were susceptible to imipenem/relebactam.

Conclusions. Imipenem/relebactam showed high rates of susceptibility in Enterobacterales and *P. aeruginosa* isolates from different sources of infection as well as depending on patients' location (ICU or non-ICU scenarios).

Keywords: Imipenem/relebactam, Spain, Multidrug-resistant, Intensive Care Unit, β-lactam/β-lactamase inhibitor combination

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Actividad de imipenem/relebactam frente a Enterobacterales y *Pseudomonas aeruginosa* en España. SMART 2016-2020

Objetivos. Determinar la sensibilidad a la nueva combinación de β-lactámico e inhibidor de β-lactamasas imipenem/relebactam en aislados clínicos procedentes de infecciones intraabdominales (IIA), urinarias (ITU), respiratorias (ITR) y bacteriemias del estudio SMART (Study for Monitoring Antimicrobial Resistance Trends) en ESPAÑA durante 2016 - 2020.

Métodos. Se determinó la CMI mediante microdilución en caldo de imipenem/relebactam y antibióticos comparadores

frente a aislados de Enterobacterales y *Pseudomonas aeruginosa*. Las CMI se analizaron empleando los puntos de corte EUCAST-2021.

Resultados. En total, se incluyeron 5.210 aislados de Enterobacterales y 1.418 aislados de *P. aeruginosa*. Imipenem/relebactam fue activo frente al 98,8% de los Enterobacterales. Distinguiendo por foco de infección, la sensibilidad fue del 99,1% en bacteriemia, del 99,2% en IIA, del 97,9% en ITR y del 99,2% en ITU. El 97,4% de los aislados procedentes de unidades de cuidados intensivos (UCI) fueron sensibles, y el 99,2% de los aislados no procedentes de UCI. En Enterobacterales, la sensibilidad frente a carbapenemasas de clase A, clase B y clase D fue del 96,2%, 15,4% y 73,2%, respectivamente. En *P. aeruginosa*, imipenem/relebactam fue activo en el 92,2% de los aislados. Distinguiendo por foco de infección, la sensibilidad frente a *P. aeruginosa* fue del 94,8% en bacteriemia, 92,9% en IIA, 91,7% en ITR y 93,1% en ITU. El 88,7% de los aislados de la UCI y el 93,6% de los aislados no procedentes de UCI fueron sensibles a imipenem/relebactam. Imipenem/relebactam fue activo frente a aislados de *P. aeruginosa* resistentes a ceftazidima (76,3%), cefepima (73,6%), imipenem (71,5%) y piperacilina/tazobactam (78,7%). Frente a los aislados de *P. aeruginosa* clasificados como MDR o DTR, el 75,1% y el 46,2%, respectivamente, fueron sensibles a imipenem/relebactam.

Conclusiones. Imipenem/relebactam mostró elevada sensibilidad frente a los aislados de Enterobacterales y *P. aeruginosa* procedentes de diferentes focos de infección, así como en función de la localización de los pacientes (UCI o no UCI).

Palabras clave: Imipenem/relebactam, España, multirresistencia, Unidad de Cuidados Intensivos, combinación de β-lactámico/inhibidor de β-lactamasa

INTRODUCTION

The growing global rising trend of antimicrobial resistance (AMR) represents a major healthcare problem, increasing mortality and healthcare costs [1]. A report from the Global Burden of Disease Study in 2019 estimates 4.95 and 1.27 million deaths associated and attributable to AMR, respectively [2]. These numbers will continue to increase, reaching 10 million attributable deaths by 2050 according to estimates from the UK government [3]. Extended-Spectrum β-lactamase (ESBL) and carbapenemase producing Enterobacterales (CPE) or carbapenem resistant *Pseudomonas aeruginosa* (CPPA), and multidrug-resistant (MDR) or difficult-to-treat resistance (DTR) are some of the resistance phenotypes with worrying public health implications, which severely limit treatment options [4–6]. In the past years, very few novel antimicrobials with novel mechanisms of action have been developed [7]. Consequently, combinations of already known antibiotics with specific enzyme-inhibitors are very valuable options. Imipenem/relebactam is a new β-lactam/β-lactamase inhibitor combination with broad spectrum activity against Ambler class A β-lactamases (including ESBL and KPC) and class C β-lactamases (AmpC) [8].

Susceptibility rates of imipenem/relebactam and comparators agents, including other β-lactam/β-lactamase inhibitor combinations, such as ceftazidime/avibactam and ceftolozane/tazobactam, were analysed against a collection of Enterobacterales and *P. aeruginosa* isolates recovered from intra-abdominal (IAI), urinary (UTI), respiratory (RTI) and bloodstream (BSI) infections in the SMART (Study for Monitoring Antimicrobial Resistance Trends) study in SPAIN during 2016 – 2020.

METHODS

Bacterial isolates. From 2016 to 2020, 11 Spanish hospitals collected up to 250 consecutive, clinically significant Gram-negative isolates per year. Sources of infection were blood, intra-abdominal, lower respiratory tract, and urinary tract. Only one isolate per Gram-negative species per patient per year was accepted. All isolates were shipped to a central laboratory (IHMA, Schaumburg, IL, USA) where identification of bacterial species was confirmed by MALDI-TOF (matrix-assisted laser desorption ionization-time of flight) before antimicrobial susceptibility testing was performed.

Antimicrobial susceptibility testing. Antimicrobial susceptibility was evaluated by broth microdilution at the central laboratory following the standard ISO recommendations**.** The antimicrobials tested were: amikacin, aztreonam, cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, colistin, ertapenem, imipenem, imipenem/relebactam, levofloxacin, meropenem, and piperacillin/tazobactam. Antimicrobial susceptibility results were interpreted using EUCAST MIC breakpoints (version 11.0, 2021) [9]. When isolates were categorized as "I" (formerly "intermediate" and now indicating "susceptible, increased exposure"), the percentage of "I" isolates were collated with "S" isolates ("susceptible, standard dose") and presented as susceptible. Multidrug-resistant (MDR) *P. aeruginosa* and Enterobacterales were defined phenotypically as those isolates resistant to any three or more of the following eight sentinel antimicrobial agents: amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, imipenem and piperacillin/tazobactam. DTR was defined as Enterobacterales or *P. aeruginosa* isolates resistant to all of the following antimicrobials: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin and levofloxacin.

Molecular characterization. Molecular testing criteria included all Enterobacterales isolates, excluding *Serratia* spp., with an imipenem or imipenem/relebactam MIC ≥2 mg/mL or a ceftolozane/tazobactam MIC ≥4 mg/mL. In *P. aeruginosa*, isolates with an imipenem or imipenem/relebactam MIC ≥4 mg/mL or a ceftolozane/tazobactam MIC ≥8 mg/mL. Molecular testing consisted on screening for β-lactamase genes encoding the metallo-β-lactamases (IMP, VIM, NDM, GIM, and SPM), serine carbapenemases [KPC, GES, and OXA-48-like (Enterobacterales) or OXA-24-like (*P. aeruginosa*)], ESBLs (SHV, TEM, CTX-M, VEB, PER, and GES), acquired AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX), and the AmpC sequence variations [*Pseudomonas*-derived cephalosporinase (PDC) variants] using published multiplex PCR assays, followed by full-gene DNA se-

quencing [10]. For *Serratia* spp., only isolates with imipenem MIC >4 mg/mL (resistant) or imipenem/relebactam MIC >2 mg/mL were screened for β-lactamase genes.

RESULTS

In total, 5,210 Enterobacterales and 1,418 *P. aeruginosa* clinical isolates were included. Distribution of species included by source of infection is detailed in Figure 1a. Globally, 37.8% of isolates were from RTI, 27.7% from IAI, 23.2% from UTI and 11.2% from BSI. MDR isolates in Enterobacterales ranged from 3.4% in *Serratia marcescens* to 28.9% in *Klebsiella aerogenes*. In *P. aeruginosa*, MDR accounted for 29.2%. Frequency of DTR isolates in Enterobacterales was low (≤1.0%) in every species, whereas 2.8% of *P. aeruginosa* isolates were DTR (Figure 1b). Differentiating the isolates from patients admitted in the Intensive Care Units (ICU), with respect to those who were not (non-ICU), MDR and DTR frequencies were higher in ICU for both Enterobacterales and *P. aeruginosa* (Figure 1c). Frequency of carbapenemase-production was as follows: *E. cloacae* (7.2%), *E. coli* (0.4%), *K. aerogenes* (1.0%), *K. pneumoniae* (12.1%), *S. marcescens* (1.7%) and *P. aeruginosa* (2.8%).

Imipenem/relebactam overall activity against Enterobacterales was 98.8%, and, distinguishing by source of infection it was 99.1% in BSI, 99.2% in IAI, 97.9% in RTI, and 99.2% in UTI. Ceftazidime/avibactam and meropenem displayed the highest susceptibility rates (≥99.0%). Table 1 shows the antimicrobial susceptibility data by species. Imipenem/relebactam was active in more than 96.4% in every single Enterobacterales species. Against CPE, imipenem/relebactam was active against 96.2% of Class A, 15.4% of Class B and 73.2% of Class D carbapenemases. With regard to the activity of other β-lactam/β-lactamase inhibitor combinations against CPE, in this study, ceftazidime/avibactam showed 100% susceptibility against Class A and Class D. Table 2 shows the susceptibility to imipenem/relebactam in ICU and non-ICU isolates as well as against MDR and DTR phenotypes. Among Enterobacterales, 97.4% of ICU isolates and 99.2% of non-ICU isolates were susceptible to imipenem/relebactam. In CPE, imipenem/relebactam was active in 59.7% and 73.2% of ICU or non-ICU isolates, respectively. However, considering only Class A CPE isolates, activity was 100% and 95.2% in ICU and non-ICU respectively. Against MDR Enterobacterales, imipenem/relebactam was active in 85.7% of ICU and 94.3% of non-ICU isolates. Activity of at least 88.9% was retained in MDR isolates resistant to 3 to 5 (out of 8) sentinel antimicrobial agents in both ICU and non-ICU scenarios. Against DTR Enterobacterales, imipenem/relebactam was only susceptible in 16.7% of non-ICU isolates.

Regarding *P. aeruginosa* the most potent agents tested were colistin (99.4%) and amikacin (94.5%). The activity of imipenem/relebactam was 92.2%, similar to ceftolozane/tazobactam (92.8%) and ceftazidime/avibactam (92.3%). Activity of imipenem/relebactam by source of infection was 94.8% in bacteraemia, 92.9% in IAI, 91.7% in RTI, and 93.1% in UTI. Imipenem/relebactam remained active against *P. aeruginosa* isolates resistant to different β-lactams, such as ceftazidime-resistant (76.3%), cefepime-resistant (73.6%), imipenem-resistant (71.5%) and piperacillin-resistant (78.7%). Of all MDR isolates, 75.1% were susceptible to imipenem/relebactam, similar to ceftolozane/tazobactam (76.3%), and higher than ceftazidime/avibactam (73.6%). Against DTR isolates, imipenem/relebactam showed 46.2% susceptibility, which was better than all other β-lactam/β-lactamase inhibitor combinations. Imipenem/relebactam was not active against carbapenemase-producers (Table 1). Among *P. aeruginosa*, 88.7% of ICU isolates and 93.6% of non-ICU isolates were susceptible to imipenem/relebactam. With respect to MDR *P. aeruginosa*, imipenem/relebactam was active in 70.6% of ICU and 77.8% of non-ICU isolates. Activity of at least 81.4% was retained in MDR isolates resistant to 3 to 4 (out of 8) sentinel antimicrobial agents in both ICU and non-ICU scenarios. Against DTR *P. aeruginosa*, imipenem/relebactam was susceptible in 38.5% and 50.0% of ICU or non-ICU isolates, respectively (Table 2).

Overall, 173 (2.6%) [62 (1.2%) Enterobacterales and 111 (7.8%) *P. aeruginosa*)] isolates were resistant to imipenem/relebactam. Resistant isolates were as follows: *E. coli* (*n*=1; VIM-1), *K. pneumoniae* [*n*=43, OXA-48 (32), VIM-1 (6), NDM-1 (4), KPC-3 (1)], *E. cloacae* [*n*=11, VIM-1 (8), OXA-48 (3)], *K. aerogenes* (*n*=2, NDM-1, one isolate not characterized), *S. marcescens* [n=5, OXA-48 (2), VIM-1 (2), one isolate not characterized] and *P. aeruginosa* [*n*=111, VIM-1 (11), VIM-2 (10), VIM-20 (7), GES-5 (7), IMP-13 (2), IMP-like (2), PER-1 (1), *Pseudomonas*-derived cephalosporinases only, PDCs (62), nine isolates not characterized]. Details of molecular characterization of resistant isolates are shown in Supplementary table 1.

DISCUSSION

Global burden of AMR is increasing worldwide causing 1.27 million attributable deaths in 2019 [2]. In addition, antibiotic consumption is continuously growing, as shown by a recent report illustrating an increase of 46% between 2000 and 2018 [11]. Nevertheless, the development of new antibiotics is not enough to mitigate the situation. Efforts should focus on innovating and developing new antimicrobials or alternative therapies, along with surveillance studies to monitor the AMR trends.

Here we present the results of the SMART surveillance study in Spain, focused on the activity of imipenem/relebactam. In this report, we have considered only the resistant isolates for MDR and DTR classifications, using the new EUCAST definitions in which susceptible isolates combine "S" category with "I" (susceptible, increased exposure) category. In other publications, the non-susceptible isolates (intermediate + resistant) are included together [12,13]. Such a difference causes variations in the total number of isolates belonging to MDR/DTR categories and in the rates of susceptibility. As an example, in this dataset, DTR isolates only represent 0.3% in Enterobacterales and 2.8% in *P. aeruginosa*. If we had considered non-susceptible isolates together (intermediate + resistant), DTR would represent 1.3% in Enterobacterales and 26.3% in *P. aeruginosa*.

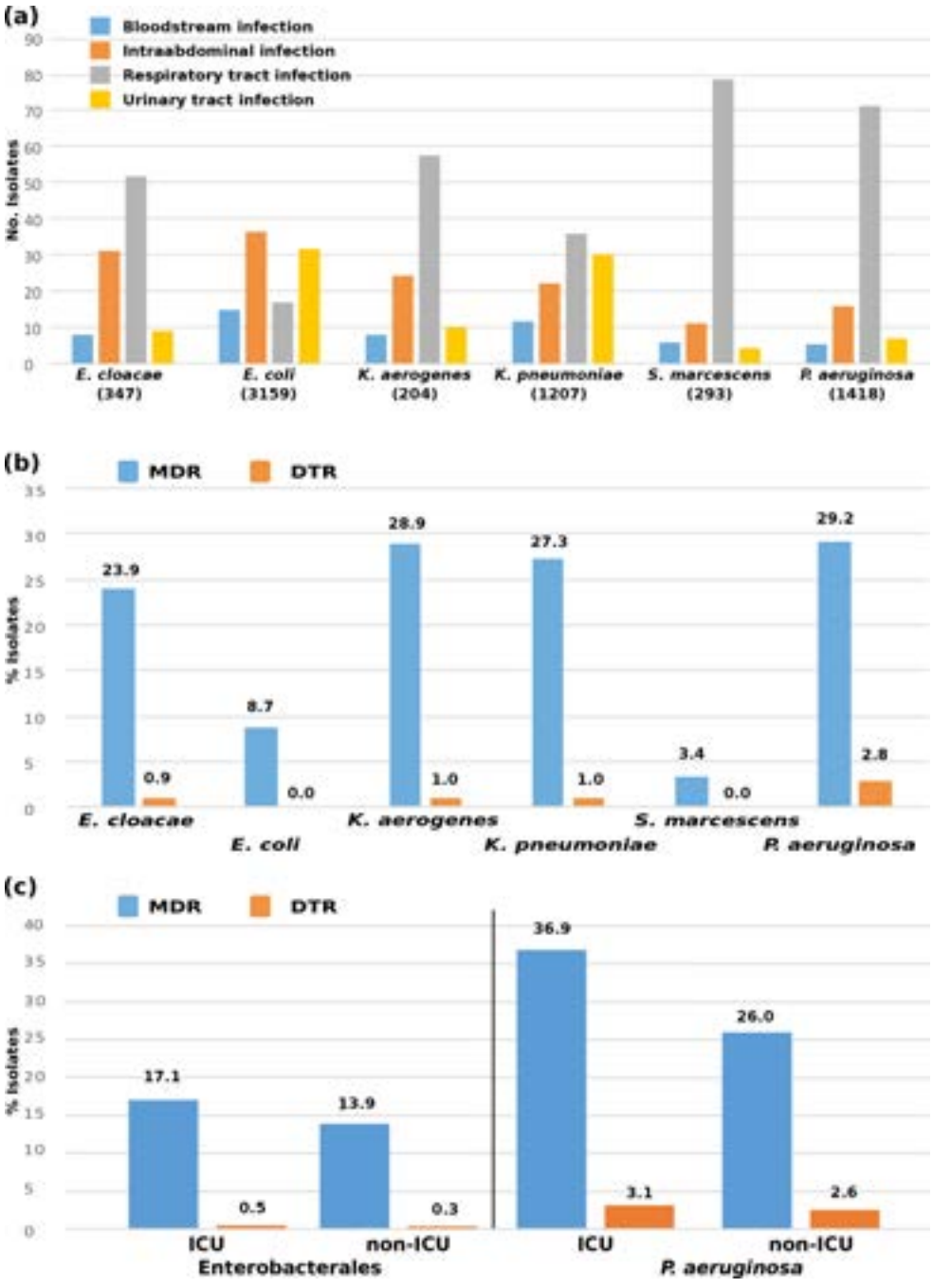

Figure 1 | **Distribution of species and MDR/DTR frequencies included in the study: a) Distribution of species included by source of infection. b) Frequencies of MDR and DTR isolates by species. c) Frequencies of MDR and DTR in ICU or non-ICU scenarios.**

MDR, multidrug-resistant; DTR, difficult-to-treat resistance; ICU, intensive care unit

In this study, imipenem/relebactam showed high activity against Enterobacterales, with susceptibility rates of 97.4% in ICU and 99.2% in non-ICU scenarios. Furthermore, it inhibited ≥97.9% of Enterobacterales regardless of infection type. These results are in agreement with previous SMART reports in Europe, that showed 98.4% and 98.5% activity in isolates from IAI and UTI [14]. Imipenem/relebactam also retains activity against Class A (96.2%) carbapenemases, which is slightly lower than a pre-

Table 1 **Antimicrobial susceptibility of imipenem/relebactam and comparator agents against Enterobacterales and *P. aeruginosa* collected in Spain from 2016 – 2020.**

Microorganism (n)	TZP	CAZ	FEP	ATM	C/T	CZA	IPM	IPR	MEM	ETP	CIP	LVX	AMK	CST
Enterobacterales (5,210)	82.7	84.7	88.1	84.3	93.9	99.5	98.7	98.1	99.2	95.1	70.5	73.0	98.1	92.6
E. coli (3,159)	89.2	90.6	92.1	89.3	99.0	100	100	99.9	99.9	99.3	67.7	68.7	98.4	99.5
K. pneumoniae (1,207)	68.2	72.0	73.0	72.6	85.4	99.4	96.4	96.4	97.3	86.5	65.0	71.4	97.1	95.0
E. cloacae (347)	73.8	73.8	89.3	76.1	80.7	96.1	96.8	96.8	97.7	84.7	86.3	86.2	99.1	90.5
K. aerogenes (204)	65.2	68.1	98.0	71.1	81.9	100	97.6	99.0	99.0	94.1	91.3	95.1	98.5	99.0
S. marcescens (293)	94.2	97.6	98.3	98.3	97.3	100	97.3	98.3	99.3	98.3	91.8	94.5	97.6	-
CPE (190)[a]	1.6	14.7	14.2	18.4	12.1	82.7	69.5	68.4	78.4	4.2	10.2	14.7	86.3	78.4
Class A (26)	7.7	3.9	7.7	0.0	3.9	100	19.2	96.2	57.7	7.7	0.0	0.0	73.1	84.6
Class B (26)	0.0	0.0	0.0	42.3	0.0	12.5	30.8	15.4	50.0	11.5	6.7	23.1	65.4	80.8
Class D (138)	0.7	19.6	18.1	17.4	15.9	100	86.2	73.2	87.7	2.2	11.4	15.9	92.8	76.8
P. aeruginosa (1,418)	68.9	72.6	74.3	80.2	92.8	92.3	73.6	92.2	87.8	-	63.6	57.4	94.5	99.4
CAZ-resistant (388)	9.3	0.0	79.9	45.4	75.0	72.3	36.9	76.3	65.7	-	37.2	27.1	85.8	99.0
FEP-resistant (364)	9.9	14.8	0.0	40.9	73.1	68.6	36.3	73.6	61.5	-	31.6	22.0	83.5	98.9
IMP-resistant (375)	28.3	34.7	38.1	55.5	78.1	79.2	0.0	71.5	56.5	-	24.7	17.1	85.9	98.9
PTZ-resistant (441)	0.0	20.2	25.6	43.1	79.1	76.7	39.0	78.7	70.0	-	36.8	24.5	88.0	99.1
MDR (414)	6.5	15.5	17.2	38.2	76.3	73.6	30.7	75.1	61.6	-	29.2	19.1	85.0	99.0
DTR (39)	0.0	0.0	0.0	0.0	41.0	37.5	0.0	46.2	0.0	-	0.0	0.0	82.1	100
CPPA (39)[b]	10.3	0.0	5.1	74.4	2.6	35.0	0.0	0.0	2.6	-	2.0	0.0	41.0	100

TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; ATM, aztreonam; C/T, ceftolozane/tazobactam; CZA, ceftazidime-avibactam; IPM, imipenem; IPR, imipenem/relebactam; MEM, meropenem; ETP, ertapenem; CIP, ciprofloxacine; LVX, levofloxacine; AMK, amikacine; CST, colistine; CPE, Carbapenemase-producing Enterobacterales; MDR, multidrug-resistant; DTR, difficult-to-treat resistance; CPPA, Carbapenemase-producing *P. aeruginosa*.

[a]Carbapenemase-producing *Enterobacterales* (CPE) included the following species and types: *E. coli* n=12 [OXA-48 (8); KPC-3 (2); KPC-type, (1); VIM-1, (1)]; *K. pneumoniae* n=146 [OXA-48 (111); OXA-244 (1); KPC-3 (21); KPC-2 (1); NDM-1 (5); VIM-1, (7)]; *E. cloacae* n=25 [OXA-48 (15); GES-6 (1); VIM-1 (9)]; *K. aerogenes* n=2 [NDM-1 (1); OXA-48 (1)]; *S. marcescens* n=5 [OXA-48 (2); VIM-1 (3)]

- **Class A: KPC-3 (23), KPC-2 (1), KPC-type (1), GES-6 (1)**
- **Class B: VIM-1 (20), NDM-5 (6)**
- **Class D: OXA-48 (137), OXA-244 (1)**

[b]Carbapenemase-producing P. aeruginosa (CPPA) included the following types: VIM-1 (11), VIM-2 (10), VIM-20 (7), IMP-13 (2), IMP-like (2), GES-5 (7)

vious Spanish surveillance report, where 100% activity was observed [15]. Regarding MDR phenotypes, imipenem/relebactam inhibited 85.7% and 94.3% of Enterobacterales of ICU and non-ICU, respectively, similar to previous reports where MDR Enterobacterales showed an activity between 93.9% – 98.1% [14,16].

Against *P. aeruginosa*, imipenem/relebactam inhibited 92.2% of isolates, a slightly lower rate than a previous Spanish multicentre study in 2017, in which 97.3% of clinical isolates where susceptible [17]. Analysing by infection type, imipenem/relebactam showed that ≥91.7% of *P. aeruginosa* isolates were susceptible. Similar results were reported in isolates from IAI (94.4%) or UTI (93.0%) in Europe [14]. Relebactam restored imipenem susceptibility in 71.5% and 75.1% of *P. aeruginosa* imipenem-resistant and MDR isolates, respectively; similar to a previous SMART study in the United States [16]. Regarding activity in ICU, imipenem/relebactam inhibited 88.7% of *P. aeruginosa*, less than non-ICU isolates (93.6%), which is partly justified by a higher rate of MDR in the ICU scenario. Imipenem/relebactam did not show activity against CPPA. Those isolates carried GES-5 or different metallo-β-lactamases, against which it does not exhibit activity [14].

While in imipenem/relebactam-resistant Enterobacterales isolates, all were CPE, in *P. aeruginosa*; only 35.1% of imipenem/relebactam-resistant isolates were CPPA. Nevertheless, without using a whole genome sequencing analysis, it is not possible to correctly characterize other implicated resistance mechanisms, especially in *P. aeruginosa*, such as mutations in the porin OprD [18,19].

Among limitations of this study included that carbapenemase production was only evaluated among isolates non-susceptible to imipenem or imipenem/relebactam or ceftolozane/tazobactam.

Table 2 **Antimicrobial susceptibility of imipenem and imipenem/relebactam against Enterobacterales and *P. aeruginosa* including MDR phenotypes in ICU and non-ICU scenarios**

	ICU		non-ICU	
Microorganism (n, ICU/n non-ICU)	IPM	IPR	IPM	IPR
Enterobacterales (1,067/4,143)	97.4	97.4	99.0	99.2
E. coli (430/2,729)	100	100	100	99.9
K. pneumoniae (299/908)	96.3	93.6	96.4	97.4
E. cloacae (124/223)	94.4	96.0	98.2	97.3
K. aerogenes (89/115)	94.4	97.8	100	100
S. marcescens (125/168)	96.0	98.4	100	98.2
CPE (67/123)	71.6	59.7	68.3	73.2
Class A (5/21)	28.6	100	19.0	95.2
Class B (14/12)	28.6	14.3	33.3	16.7
Class D (48/90)	89.6	68.8	84.4	75.6
MDR total (182/574)	86.3	85.7	93.2	94.3
MDR 3* (59/189)	100	96.6	100	99.5
MDR 4 (28/179)	82.1	89.2	98.9	98.9
MDR 5 (63/155)	88.9	88.9	93.5	95.5
MDR 6 (26/39)	69.2	65.4	56.4	61.5
MDR 7 (5/12)	20.0	20.0	25.0	33.3
MDR 8 (1/0)	0.0	0.0	-	-
DTR (5/12)	0.0	0.0	0.0	16.7
P. aeruginosa (415/1,003)	63.1	88.7	77.9	93.6
CAZ-resistant (139/249)	29.5	71.9	41.0	78.7
FEP-resistant (133/231)	31.6	69.9	39.0	75.8
IMP-resistant (153/222)	-	71.2	-	71.6
PTZ-resistant (163/278)	33.7	72.4	42.1	82.4
MDR total (153/261)[a]	26.1	70.6	33.3	77.8
MDR 3 (23/55)	43.5	82.6	49.1	94.5
MDR 4 (46/70)	50.0	89.1	57.1	81.4
MDR 5 (59/80)	11.9	64.4	21.3	75.0
MDR 6 (23/47)	0.0	39.1	4.3	63.8
MDR 7 (2/7)	0.0	50.0	14.3	28.6
MDR 8 (0/2)	0.0	-	0.0	-
DTR (13/26)	0.0	38.5	0.0	50.0
CPPA (15/24)	0.0	0.0	0.0	0.0

ICU, intensive care unit; IPM, imipenem; IPR, imipenem/relebactam; CPE, Carbapenemase-producing *Enterobacterales*; MDR, multidrug-resistant; DTR, difficult-to-treat resistance; CPPA, Carbapenemase-producing *P. aeruginosa*.

[a]MDR nº, resistant to 3/4/5/6/7 or 8 of the eight sentinel antimicrobial agents

In conclusion, imipenem/relebactam showed high rates of susceptibility in Enterobacterales and *P. aeruginosa* isolates from different sources of infection as well as depending on patients' location (ICU or non-ICU scenarios). These results place imipenem/relebactam as an attractive therapeutic option to alternate with already marketed β-lactam/β-lactamase inhibitor combinations and ensure that antimicrobial stewardship is preserved.

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CONFLICTS OF INTEREST

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REFERENCES

1. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist 2019;12:3903–10. doi: 10.2147/IDR.S234610
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022 12;399:629–55. doi: 10.1016/S0140-6736(21)02724-0
3. Tackling drug-resistant infections globally : final report and recommendations / the Review on Antimicrobial Resistance chaired by Jim O'Neill. doi: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf Accessed 05 February 2023.
4. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018;67(12):1803-1814. doi: 10.1093/cid/ciy378.
5. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "Sell-By Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clin Infect Dis. 2020;71:1776–82. doi: 10.1093/cid/ciaa122
6. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81. doi: 10.1111/j.1469-0691.2011.03570.x
7. Talbot GH, Jezek A, Murray BE, Jones RN, Ebright RH, Nau GJ, et al. The Infectious Diseases Society of America's 10 × '20 Initiative (10 New Systemic Antibacterial Agents US Food and Drug Administration Approved by 2020): Is 20 × '20 a Possibility? Clin Infect Dis 2019;18;69:1–11. doi: 10.1093/cid/ciz089
8. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. J Antimicrob Chemother 2013;68:2286–90. doi: 10.1093/jac/dkt178
9. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org.
10. Nichols WW, de Jonge BLM, Kazmierczak KM, Karlowsky JA, Sahm DF. In Vitro Susceptibility of Global Surveillance Isolates of *Pseudomonas aeruginosa* to Ceftazidime-Avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 2016;60:4743–9. doi: 10.1128/AAC.00220-16
11. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health 2021;5:e893–904. doi: 10.1016/S2542-5196(21)00280-1
12. Karlowsky JA, Lob SH, Raddatz J, DePestel DD, Young K, Motyl MR, et al. In Vitro Activity of Imipenem/Relebactam and Ceftolozane/Tazobactam Against Clinical Isolates of Gram-negative Bacilli With Difficult-to-Treat Resistance and Multidrug-resistant Phenotypes-Study for Monitoring Antimicrobial Resistance Trends, United States 2015-2017. Clin Infect Dis 2021;15;72:2112–20. doi: 10.1093/cid/ciaa381
13. Torrens G, van der Schalk TE, Cortes-Lara S, Timbermont L, del Barrio-Tofiño E, Xavier BB, et al. Susceptibility profiles and resistance genomics of *Pseudomonas aeruginosa* isolates from European ICUs participating in the ASPIRE-ICU trial. J Antimicrob Chemother. 2022;29;77:1862-1872 doi: 10.1093/jac/dkac122
14. Lob SH, Karlowsky JA, Young K, Motyl MR, Hawser S, Kothari ND, et al. In vitro activity of imipenem-relebactam against resistant phenotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance Europe 2015–2017. J Med Microbiol. 2020;69:207–217. doi: 10.1099/jmm.0.001142
15. Vázquez-Ucha JC, Seoane-Estévez A, Rodiño-Janeiro BK, González-Bardanca M, Conde-Pérez K, Martínez-Guitián M, et al. Activity of imipenem/relebactam against a Spanish nationwide collection of carbapenemase-producing Enterobacterales. J Antimicrobial Chemother. 2021;76:1498–1510. doi: 10.1093/jac/dkab043
16. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In-vitro activity of imipenem/relebactam and key ß-lactam agents against Gram-negative bacilli isolated from lower respiratory tract infection samples of intensive care unit patients – SMART Surveillance United States 2015–2017. Int J Antimicrob Agents. 2020;55:105841. doi: 10.1016/j.ijantimicag.2019.10.022
17. Fraile-Ribot PA, Zamorano L, Orellana R, López-Causapé C, Cabot G, Bou G, et al. Activity of Imipenem-Relebactam against a Large Collection of *Pseudomonas aeruginosa* Clinical Isolates and Isogenic B-Lactam-Resistant Mutants. Antimicrobial Agents and Chemotherapy 2020;64:6. doi: 10.1128/AAC.02165-19.
18. Gomis-Font MA, Cabot G, Sánchez-Diener I, Fraile-Ribot PA, Juan C, Moya B, et al. In vitro dynamics and mechanisms of resistance development to imipenem and imipenem/relebactam in *Pseudomonas aeruginosa*. J. Antimicrobial Chemother. 2020;75:2508–2515. doi: 10.1093/jac/dkaa206

19. Young K, Painter RE, Raghoobar SL, Hairston NN, Racine F, Wisniewski D, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa.* BMC Microbiol 2019 4;19:150. doi: 10.1186/s12866-019-1522-7

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Brief report

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Epidemiology and prevalence of mutations associated with resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium* in a tertiary hospital from Madrid, Spain

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ABSTRACT

Objectives. *Mycoplasma genitalium* causes persistent sexually transmitted infections. The aims of this study were to estimate the prevalence of resistances to macrolides and fluoroquinolones in *M. genitalium* and the sexually transmitted coinfections in patients at Hospital Universitario La Paz (Madrid, Spain).

Material and methods. Patients attended between January and October 2021 were studied. Screening for sexually transmitted pathogens and detection of 23S rRNA and *parC* genes mutations were performed by real-time PCR (Allplex, Seegene™).

Results. A total of 1,518 females and 1,136 males were studied. The prevalence of *M. genitalium* was 2.1%. The macrolides resistance rate was 51.8%. The mutations found were A2059G, A2058T and A2058G. The rate of resistance to fluoroquinolones was 17.8% being the G248T mutation (S83I) the most frequent. Seven males had some sexual transmitted coinfection.

Conclusions. Although the percentage of *M. genitalium* infections is low, the high rate of resistance to macrolides makes it necessary to revise the protocols for diagnosis and empirical treatment of sexually transmitted infections. The use of fluoroquinolones is appropriate after screening of macrolide resistance profile.

Keywords: *Mycoplasma genitalium*, macrolides, coinfection, azithromycin, fluoroquinolones, moxifloxacin, resistance, mutation, STI

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Epidemiología y prevalencia de mutaciones asociadas a la resistencia a macrólidos y fluoroquinolonas en *Mycoplasma genitalium* en un hospital terciario de Madrid, España

RESUMEN

Objetivos. *Mycoplasma genitalium* causa infecciones de transmisión sexual persistentes. Los objetivos de este trabajo fueron estimar la prevalencia de resistencias a macrólidos y fluoroquinolonas en *M. genitalium* así como las coinfecciones de transmisión sexual en pacientes del Hospital Universitario La Paz (Madrid, España).

Material y métodos. Se estudiaron pacientes atendidos entre enero y octubre de 2021. El cribado de patógenos de transmisión sexual y la detección de mutaciones de los genes ARNr 23S y *parC* se realizaron por PCR en tiempo real (Allplex, Seegene™).

Resultados. Se estudiaron 1.518 mujeres y 1.136 hombres. La prevalencia de *M. genitalium* fue del 2,1%. La tasa de resistencia a macrólidos fue del 51.8%. Las mutaciones encontradas fueron A2059G, A2058T y A2058G. La tasa de resistencias a fluoroquinolonas fue del 17.8% siendo la mutación G248T (S83I) la más frecuente. Siete hombres presentaron alguna coinfección de transmisión sexual.

Conclusiones. Aunque el porcentaje de infecciones por *M. genitalium* es bajo, la elevada tasa de resistencias frente a macrólidos hace necesario modificar los protocolos de diagnóstico y tratamiento empírico de las infecciones de transmisión sexual. El uso de fluoroquinolonas es adecuado tras testar previamente el perfil de resistencia a macrólidos.

Palabras clave: *Mycoplasma genitalium*, macrólidos, coinfección, azitromicina, fluoroquinolonas, moxifloxacino, resistencia, mutación, ITS

INTRODUCTION

Mycoplasma genitalium (MG) is a sexually transmitted pathogen that mainly affects males causing persistent non-gonococcal urethritis [1]. Some studies have reported cases of proctitis or epididymitis in males with a high bacterial load [2]. The prevalence of MG infections in females is lower than males. Several reports have associated the detection of MG with pelvic inflammatory disease, cervicitis, premature rupture of membranes or miscarriage but there is no conclusive data [3]. *M. genitalium* has been detected in a high percentage of asymptomatic patients. However, according to the therapeutic guidelines for the management of sexually transmitted diseases, these patients should not be screened for MG detection [4].

In recent years, there has been an increase in MG resistances reported in different countries worldwide [5]. The prevalence of mutations associated with resistance to macrolides (MARM) or fluoroquinolones (MARF) contrasts between series depending of the local epidemiology [6-9]. A meta-analysis estimated the overall prevalence of MARM and MARF at 19% and 3.5% respectively, and dual resistance at 2% in Spain [5]. Resistance data in MG have been reported in different communities of Spain but there are no data from the Community of Madrid since 2015 [10].

The resistance of MG is due to mutations in the region V of the 23S rRNA gen level conferring resistance to macrolides or some mutations of the topoisomerase IV *parC/gyrA* genes level producing resistance to fluoroquinolones. Although the detection of MARM implies resistance to treatment, the detection of MARF does not always imply a therapeutic failure [6]. The treatment of choice for MG infections is azithromycin as first line followed by moxifloxacin as second line of treatment. However, different MG guidelines show the need to detect the presence of mutations to macrolides for anticipate the treatment failure and clinical complications in symptomatic patients [4].

The aim of the study was to estimate the prevalence of MG in patients at Hospital Universitario La Paz (HULP) between January and October 2021. For positive MG patients, the prevalence of MARM and MARF, percentage of previous treatment with macrolides or fluoroquinolones and the prevalence of sexually transmitted coinfections (STCs) were calculated.

MATERIAL AND METHODS

In a retrospective observational cohort study design, we collected the demographic, analytical and previous treatments data of patients with MG detection from the HULP database and laboratory informatics systems.

The reference method for MG resistance detection has been Sanger sequencing of genes. However, automated commercial kits are now available and allow a rapid detection of MG resistances by real time polymerase chain reaction (RT-PCR).

Genitourinary samples (first-void urines, rectal or vaginal swabs) were screened for sexual transmitted infections using RT-PCR (Allplex™ 7 STI Essential Assay, Seegene®, Seoul, Republic of Korea) including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitallium*, among others. Positive samples for MG were screened for detection of MARM and MARF. The resistances to macrolides were detected with the Allplex™ MG & AziR Assay including six mutations: A2058C, A2058G, A2058T, A2059C, A2059G and A2059T. Mutations associated with fluoroquinolones resistances were detected with Allplex™ MG & MoxiR Assay (Seegene®) including another six mutations against *parC* gene: A247C (S83R), G248A (S83N), G248T (S83I), G259A (D87N), G259C (D87H) and G259T (D87Y). The RT-PCRs were performed in combination with automated DNA extraction and PCR setup using a Microlab STARlet Liquid Handling robot (Hamilton®), according to the manufacturers' instructions and CFX96 Touch Real-Time PCR Detection System thermal cycler (BioRad®,Hercules, California).

No ethical review or approval was required for the study on human participants in accordance with institutional requirements of the retrospective studies. The data collected were obtained from clinical samples that were necessary for the clinical diagnosis of the patients.

RESULTS

During the study period 2,654 patients were screened for MG (1,518 were females and 1,136 were males) of which 56 patients (~2.1%) were positive, including 41 first-void urines (73.2%), 14 rectal swabs (25%) and one vaginal swab (1.8%).

The mean age of our patients was 31 years IQR (25-34), 44/56 patients were males (78.6%) and 12/56 patients were females (21.4%). Seven males (12.5%) of our study had some STCs with *N. gonorrhoeae* (n=4/56) or *C. trachomatis* (n=3/56) during the differential diagnosis.

The table 1 describes the mutations associated with resistance to macrolides and fluoroquinolones detected in relation with the samples analyzed, the previous treatment of patients with azithromycin or moxifloxacin, and the STCs.

Out of 56 isolates analyzed, twenty-three strains (41.1%) were classified as *wild type* strains. Twenty-nine strains out of 56 (51.8%) had mutations that conferring resistance to macrolides. The most detected MARM was A2059G in 11 out of 29 strains (36.6%) following by A2958T mutation (n=10/29, 34.5%). One out of 29 strains resistance to macrolides showed two mutations in A2058G and A2059G. Seventeen (58.6%) out of the 29 patients with macrolides resistance had not been previously treated with azithromycin, ten (34.5%) of the 29 patients had received prior treatment and in two cases no record was found.

Ten out of 56 strains (17.8%) had some mutations that conferring resistance to fluoroquinolones. The most detected MARF was G248T (S83I) in 6 (60%) out of 10 strains. Five (50%) out of the 10 patients with some fluoroquinolones resistance had not been previously treated with moxifloxacin, four (40%) had received prior treatment and in one case had no record.

Table 1 **Resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium* (n=56)**

PCR-resistance	Previous treatment	Patients (%)	Samples positive (n)	Patients with STCs (n)
Wild-type MG strains	N/A	23	(19) Urine, (3) Rectal, (1) Vaginal	(1) NG, (2) CT
Macrolide resistance MG strains	10	29	29	N/A
A2059G	3	10 (34.5%)	(6) Urine, (4) Rectal	(1) NG
A2058T	4	10 (34.5%)	(6) Urine, (4) Rectal	(2) NG, (1) CT
A2058G	2	8 (27.6%)	(7) Urine, (1) Rectal	N/A
A2058G + A2059G	1	1 (3.4%)	(1) Urine	N/A
Fluoroquinolones resistance MG strains*	4	10	10	N/A
G259T (D87Y)	1	2 (20%)	(2) Urine	N/A
G248T (S83I)	2	6 (60%)	(4) Urine, (2) Rectal	N/A
A247C (S83R)	N/A	1 (10%)	(1) Rectal	N/A
G259A (D87N)	1	1 (10%)	(1) Urine	N/A

STCs: sexual transmitted coinfections; NG: *Neisseria gonorrhoeae*; CT: *Chlamydia trachomatis*; N/A: not applied
***Amino acid position changes are reported according to the amino acid positions within the MG G37 genome**

Dual mutations conferring resistance to macrolides and fluoroquinolones were detected also in ten strains (17.8%): three A2059G/G248T (30%), three A2058G/G259T (30%), two A2058G/G259T (20%), one A2059G/A247C (10%) and one A2058T/G259A (10%).

DISCUSSION

According to other studies, the highest prevalence of MG in HULP was detected in males of sexually active age. In our study, we found a higher prevalence of resistances to macrolides and fluoroquinolones than in other areas of Spain [6-9]. However, we have not found any predominant resistance mutations in patients with any STCs.

Studies reported in other areas of Spain showed a prevalence of macrolides resistance in MG of around 25-30% [6-9]. These data may be biased between studies by the overall number of patients screened for MG, the number of MG strains tested, the clinical patient condition or the use of macrolides in each health area. Our high MARM detected could be explained by the use of empirical treatment with azithromycin (1g single dose) in our area until 2022 for urethritis.

In our studio, a higher percentage of mutation A2058T macrolide resistance-associated was detected than in other series which the A2058G or A2059G mutations are the most frequent detected [6-8]. A higher prevalence of the A2058T mutation was also reported by Asenjo et al. in Spain or Braam et al. in Netherlands [9,10]. In future studies, it would be necessary to investigate the phylogenetic relationship between A2058T isolates.

In relation to fluoroquinolones resistance, there are few data available due to the short time of commercial kits have been on the market. In some studies from Spain, the prevalence of MARF is reported around 10% [6,7,8]. Our data shows a higher prevalence, however the number of strains tested was low (n=10) to infer globally in our population. However, mutations in the *gyrA* gene were not detected with this commercial kit, so there may be underdiagnosis in the detection of MARF. Furthermore, the detection of mutations relationship with fluoroquinolones resistance is not always associated with therapeutic failure [6].

Analysis of dual resistance to macrolides and fluoroquinolones did not give any group of mutations more prevalent than the others as suggested by other studies [6].

Most of the patients in our study with any macrolides or fluoroquinolones resistance had not received prior treatments. However, it should be noted that non-electronic prescriptions, treatments in clinics specialist in sexually transmitted diseases or single-dose treatments with azithromycin in emergency departments were not recorded in our informatic laboratory system. Therefore, there is probably an underestimation of patients previously treated with macrolides or fluoroquinolones in our area.

This study has some limitations, such as the lack of clinical data or information on patients' sexual practices, and analysis of post-treatment control. However, the reported data support that empirical use of azithromycin is not adequate for the treatment of MG infections in our population. As determined by the STI guidelines, prior to the detection of macrolides resistance, the empirical treatment should be with doxycycline (100mg/12h) to reduce the MG load and then, after the macrolide's resistance profile is known, switched the

treatment to azithromycin or moxifloxacin [11].

Future studies are needed to evaluate the impact of these measures in the prevalence of resistances to macrolides and fluoroquinolones.

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None to declare

CONFLICT OF INTEREST

The authors declare no have conflict of interest

REFERENCES

1. Gnanadurai R, Fifer H. *Mycoplasma genitalium*: A Review. *Microbiology (Reading).* 2020;166(1):21-29. doi:10.1099/mic.0.000830
2. Bissessor M, Tabrizi SN, Bradshaw CS, et al. The contribution of *Mycoplasma genitalium* to the aetiology of sexually acquired infectious proctitis in men who have sex with men. Clin Microbiol Infect. 2016;22(3):260-265. doi:10.1016/j.cmi.2015.11.016
3. Lis R, Rowhani-Rahbar A, Manhart LE. Mycoplasma genitalium infection and female reproductive tract disease: a meta-analysis. Clin Infect Dis. 2015;61(3):418-426. doi:10.1093/cid/civ312
4. Soni S, Horner P, Rayment M, et al. British Association for Sexual Health and HIV national guideline for the management of infection with *Mycoplasma genitalium* (2018). Int J STD AIDS. 2019;30(10):938-950.
5. Machalek DA, Tao Y, Shilling H, et al. Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium*: a systematic review and meta-analysis. Lancet Infect Dis. 2020;20(11):1302-1314. doi:10.1016/S1473-3099(20)30154-7
6. de Salazar A, Barrientos-Durán A, Espadafor B, Fuentes-López A, Chueca N, Garcia F. Macrolide and fluoroquinolone resistance of *Mycoplasma genitalium* in southern Spain, 2018-2019. Sex Transm Infect. 2021;97(1):8-10. doi:10.1136/sextrans-2019-054386
7. Rivaya B, Le Roy C, Jordana-Lluch E, et al. Detection and Prevalence of Macrolide and Fluoroquinolone Resistance in *Mycoplasma genitalium* in Badalona, Spain. Antibiotics *(Basel).* 2022;11(4):485. doi:10.3390/antibiotics11040485
8. Lucena Nemirosky J, Espelt R, López Grado E, et al. Macrolide resistance in Mycoplasma genitalium in Catalonia, Spain: a 1 year prospective study. J Antimicrob Chemother. 2021;76(10):2702-2707. doi:10.1093/jac/dkab224
9. Asenjo A, Kusters JG, Severs TT, Alós JI. *Mycoplasma genitalium* in Spain: prevalence of genital infection and frequency of resistance to macrolides. Enferm Infecc Microbiol Clin (Engl Ed). 2018;36(3):169-171. doi:10.1016/j.eimc.2017.01.006
10. Braam JF, Slotboom B, Van Marm S, et al. High prevalence of the A2058T macrolide resistance-associated mutation in *Mycoplasma genitalium* strains from the Netherlands. J Antimicrob Chemother. 2017;72(5):1529-1530. doi:10.1093/jac/dkw584
11. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep. 2021;70(4):1-187. doi: 10.15585/mmwr.rr7004a1.

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Carta al Director

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Absceso por *Clostridium perfringens* en usuario de drogas por vía parenteral: slamming

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Varón de 56 años homosexual (HSH) procedente de España que acude a urgencias por presencia de lesión cutánea abscesificada en el antebrazo izquierdo de dos días de evolución dolorosa al tacto, eritematosa, caliente y con aumento progresivo del volumen sin presencia de fiebre (36,2°C) ni signos sistémicos de infección. La lesión cutánea se produjo en el punto de venopunción de drogas inyectables días anteriores.

Como antecedentes previos de interés cabe destacar que se trataba de un paciente en riesgo de exclusión social y conductas sexuales de riesgo con diagnóstico previo de sífilis (RPR negativo), hepatitis A (VHA) con resolución espontánea, hepatitis B y C (VHB, VHC) resueltas con tratamiento farmacológico, citología anal positiva para virus del papiloma humano genotipos 35 y 59, junto con uretritis y proctitis por *Chlamydia trachomatis* en resolución. Diagnosticado de VIH años previos con buen control (carga viral <20 copias/mL, CD4: 328/µL) en tratamiento con Dovato (dolutegravir/lamivudina) 300/50mg. Presentaba historia previa de seguimiento en Centro de Atención a las Adicciones (CAD).

Durante la entrevista en el servicio de urgencias el paciente aseguró haber practicado días antes sesión de *"chemsex"* [1] donde consumió éxtasis líquido (GHB) y mefedrona además de realizar *"slam"* [2] consumiendo ketamina por vía intravenosa (UDVP) sin utilización de métodos de barrera. En los últimos años se ha producido un incremento entre la población HSH de las reuniones grupales sexuales ("*chills*") [1-3] para mantener relaciones sexuales bajo los efectos de drogas por vía oral, inhalada o esnifada (*chemsex*) o por vía parenteral (*slam*) [2]. El consumo de drogas en población HSH para mantener relaciones sexuales está directamente relacionado con la disminución del uso del preservativo y con el incremento de enfermedades de transmisión sexual destacando la primoinfección por VIH [3].

En urgencias se llevó a cabo el drenaje, bajo anestesia local, del absceso tras incisión con salida de material purulento, así como una serología de control frente VHC, VHB, VIH, y sífilis. El paciente fue dado de alta con tratamiento empírico con clindamicina oral 300mg cada 6 horas durante 10 días además

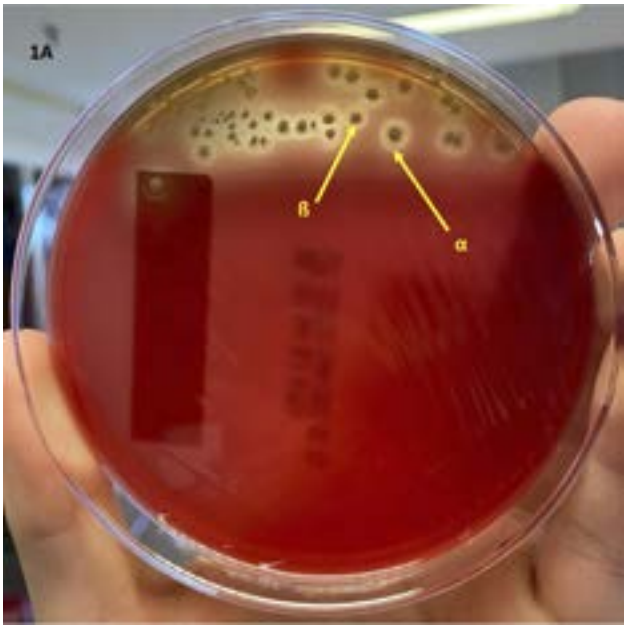

Figura 1A **Agar sangre-alcohol feniletílico con cultivo puro de *Clostridium perfringens*. Se observa la doble hemólisis: las flechas amarrillas indican la hemólisis completa interna (ß) y la hemólisis externa incompleta (α) alrededor de las colonias características de esta especie.**

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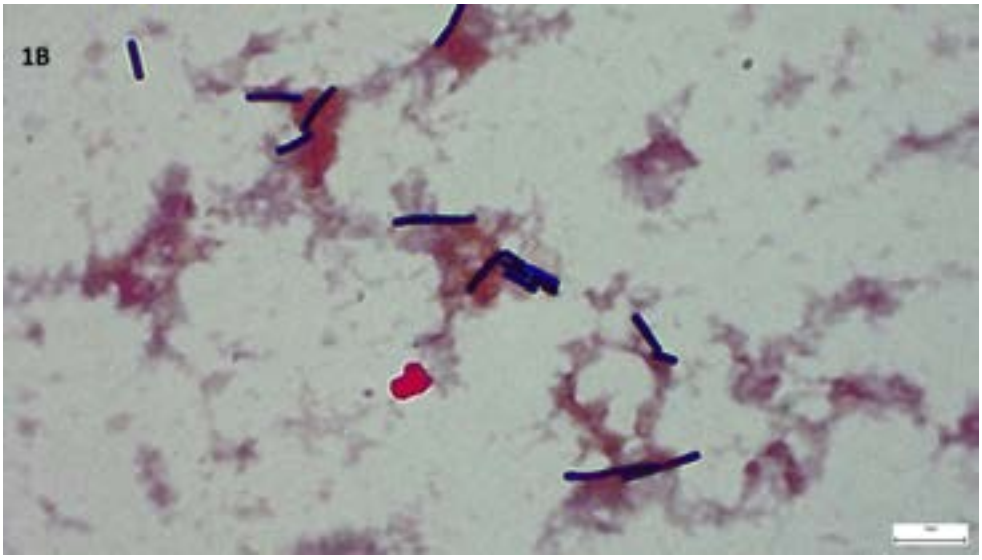

Figura1B | **Tinción de gram directa de la muestra donde se observa la presencia de bacilos gram positivos en forma de "ladrillo" o "furgón" sugestivos de *Clostridium* spp.**

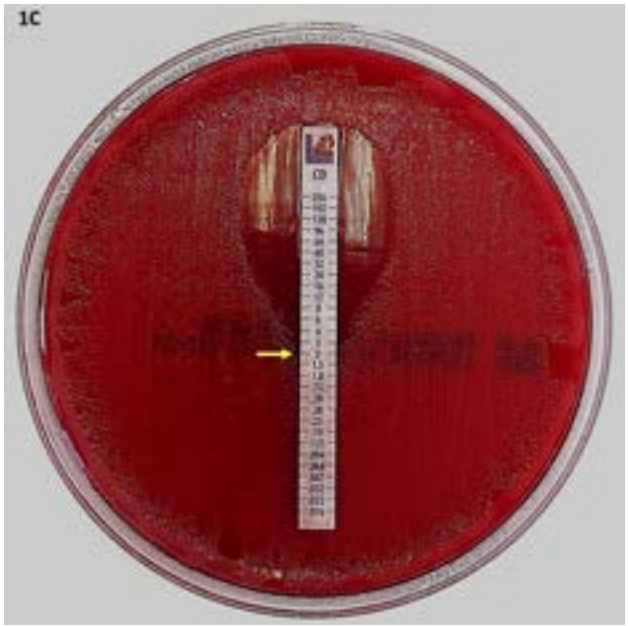

Figura 1C | **E-test a clindamicina de *C. perfringens* en agar Brucella con CMI 2 mg/L (flecha amarilla) (punto de corte CMI 0,25 mg/L) que muestra la cepa resistente.**

de curas locales y tratamiento analgésico a demanda. La pauta de clindamicina oral se debió a la frecuente infección de piel y partes blandas por *Staphylococcus aureus* y la cobertura por una posible cepa de *S. aureus* resistente a meticilina (SARM).

El absceso se sembró en medios generales aerobios agar sangre y agar chocolate, así como en medio selectivo agar MacConkey (Becton Dickinson®, BD) y medio de enriquecimiento tioglicolato. Además, se sembró en medios anaerobios como agar Brucella, agar KV (kanamicina-vancomicina agar sangre) y agar PEA (alcohol feniletílico agar sangre) (BD).

Se llevo a cabo tinción de gram directa de la muestra observándose bacilos gram positivos grandes (~4 μm) con forma de "ladrillo" (Figura 1A). Tras 72h de incubación en estufa a 37°C con 5% de CO_2 en el caso de los medios aerobios, todas las placas fueron estériles. Sin embargo, en el caso de los medios anaerobios tras incubación a 37°C con atmósfera en ausencia de oxígeno con recipientes GasPak EZ (BD) durante 48h se dio lugar a la presencia en agar PEA de un cultivo puro colonias grandes, opacas, sin velo y con doble hemólisis: hemólisis interna completa (β) y hemólisis externa no completa (α) (Figura 1B). La identificación con el sistema Matrix Assisted Laser Desorption/Ionization-Mass Spectrometry (MALDI-TOF MS, Brukerr®) dio lugar a la identificación de *Clostridium perfringens* con un score de 2,15.

Se llevó a cabo el estudio de sensibilidad antibiótica de la cepa mediante técnica épsilon test (E-test) en agar Brucella con sensibilidad a penicilina (0,06 mg/L), amoxicilina (0,012 mg/L), amoxicilina/clavulánico (0,012 mg/L), piperacilina/tazobactam (0,06 mg/L), imipenem (0,12 mg/L), vancomicina (0,5 mg/L) y metronidazol (1 mg/L). El aislado fue resistente a clindamicina con una CMI de 2 mg/L (punto de corte en 0,25 mg/L siguiendo los puntos de corte EUCAST 2022 versión 12.0) (Figura 1C). Aunque varía entre estudios reportados, únicamente entre un 2-10% de las cepas de *C. perfringes* muestran resistencia *in vitro* a clindamicina [4,5]. El resultado de las serologías realiza-

das en urgencias fueron negativas excepto para VHC que fue positiva (genotipo 1a) con carga viral de 72.400 UI/mL.

El aislamiento de algunas especies de *Clostridium* spp. puede representar contaminación de heridas [6]. Sin embargo, la infección por *C. perfringes* se produce como consecuencia de la inoculación directa de los microorganismos ambientales por técnicas no asépticas entre UDVP, situación que se ve favorecida durante las reuniones de *slam* junto con otras infecciones de transmisión sanguínea como la hepatitis C [7]. El paciente fue tratado con Maviret (glecaprevir/pibrentasvir) 100/40 mg durante 8 semanas.

La infección por *C. perfringes* puede complicarse en algunas ocasiones produciendo celulitis crepitante, gangrena gaseosa e incluso mionecrosis [8].

Tras 21 días el paciente acudió de nuevo a urgencias por complicación de la lesión inicial en la zona de venopunción. El paciente presentaba dolor a la palpación en el miembro superior izquierdo, signos flogóticos, nódulo indurado-gomoso menor de 2 cm eritematoso, así como supuración espontánea de la lesión sin presentar síntomas sistémicos. Tras ecografía cutánea se determino una lesión compatible con tromboflebitis superficial sobreinfectada que afectaba a la dermis con trayectos fistulosos. Se envió nueva muestra para microbiología que resultó estéril y se pautó amoxicilina/clavulánico 875mg/125mg durante 10 días junto con utilización de heparina de bajo peso molecular 10.000 UI/24h con resolución del cuadro clínico y seguimiento por hepatitis C en tratamiento hasta negativización de la carga viral.

En resumen, el paciente presentó una tromboflebitis abscesificada en el brazo izquierdo por utilización de drogas por vía parenteral (slamming) con complicación local por una cepa de *C. perfringes* resistente a clindamicina junto con una reinfección por VHC genotipo 1a durante la relación de riesgo.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

BIBLIOGRAFÍA

1. Maxwell S, Shahmanesh M, Gafos M. Chemsex behaviours among men who have sex with men: A systematic review of the literature. Int J Drug Policy. 2019;63:74-89. doi: 10.1016/j.drugpo.2018.11.014
2. Schreck B, Victorri-Vigneau C, Guerlais M, Laforgue E, Grall-Bronnec M. Slam Practice: A Review of the Literature. Eur Addict Res. 2021;27(3):161-78. doi:10.1159/000511897
3. Ayerdi Aguirrebengoa O, Vera Garcia M, Puerta López T, et al. Changes in the profile of newly HIV-diagnosed men who have sex with men, Madrid, 2014 to 2019. Euro Surveill. 2021;26(47):2001501. doi:10.2807/1560-7917.ES.2021.26.47.2001501
4. Khanna N. Clindamycin-resistant Clostridium perfringens cellulitis. J Tissue Viability. 2008;17(3):95-97. doi:10.1016/j.jtv.2008.04.001
5. Roberts SA, Shore KP, Paviour SD, Holland D, Morris AJ. Antimicrobial susceptibility of anaerobic bacteria in New Zealand: 1999-2003. J Antimicrob Chemother. 2006;57(5):992-998. doi:10.1093/jac/dkl052
6. Rood JI, Cole ST. Molecular genetics and pathogenesis of Clostridium perfringens. Microbiol Rev. 1991;55(4):621-648. doi:10.1128/mr.55.4.621-648.1991
7. Dolengevich-Segal H, Rodríguez-Salgado B, Gómez-Arnau J, Sánchez-Mateos D. Severe Psychosis, Drug Dependence, and Hepatitis C Related to Slamming Mephedrone. Case Rep Psychiatry. 2016;2016:8379562. doi:10.1155/2016/8379562
8. Assadian O, Assadian A, Senekowitsch C, Makristathis A, Hagmüller G. Gas gangrene due to Clostridium perfringens in two injecting drug users in Vienna, Austria. Wien Klin Wochenschr. 2004;116(7-8):264-267. doi:10.1007/BF03041058

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Carta al Director

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Primer brote de *Clostridioides difficile* ribotipo 027 en Canarias

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La infección por *Clostridioides difficile* es la principal causa de diarrea infecciosa hospitalaria y está asociada con una elevada tasa de morbilidad y mortalidad [1]. La producción de esporas altamente resistentes es la principal vía de transmisión de este patógeno en el entorno hospitalario, ya que se encuentran tanto en superficies, como en las manos del personal sanitario que no se las lava adecuadamente [1,2].

En un estudio realizado en 2012-2013, la cepa hipervirulenta de *C. difficile* toxigénico ribotipo 027 (CDTR027) fue la más prevalente en Europa (19%). Sin embargo en el caso de España, dicha cepa fue poco frecuente [3].

El Hospital Universitario Insular de Gran Canaria es un hospital de tercer nivel que comprende 538 camas y atiende a la población sur/este de la isla de Gran Canaria. En el verano de 2018 se detectó el primer brote de CDTR027 que afectó a un total de 6 pacientes. Dichos pacientes coincidieron en la planta del Servicio de Digestivo entre el 31 de julio y 7 de agosto.

El primer caso fue una mujer de 65 años natural de Alemania, que ingresó en nuestro hospital por un cuadro de cirrosis hepática descompensada. La paciente había estado ingresada cuatro meses antes en un hospital alemán, debido a una hemorragia digestiva aguda. Ante una sospecha de infección urinaria, se trató con ceftriaxona y desarrolló diarreas.

El segundo episodio fue una mujer de 66 años, trasplantada renal, ingresada por pancreatitis aguda grave. Esta compartía habitación con el primer caso y desarrolló diarreas dos días después de este, tras ser tratada con piperacilina-tazobactam.

El tercer paciente fue un varón de 77 años que estaba ingresado en la habitación contigua a las dos anteriores por una pancolitis inespecífica. Tras recibir ciprofloxacino y metronidazol por una monoartritis de rodilla, desarrolló diarreas 6 días después del primer caso. Dicho paciente requirió ingreso en la Unidad de Medicina Intensiva (UMI) y una colectomía total, tras sufrir un megacolon tóxico.

El cuarto fue una mujer de 73 años ingresada por un melanoma metastásico, que tras recibir tratamiento con ceftriaxona, hizo diarreas y rectorragia 8 días después del primer caso.

El quinto paciente fue un varón de 77 años ingresado por colecistitis aguda litiásica, en tratamiento con ciprofloxacino y ertapenem. Inicialmente el paciente evolucionó favorablemente, pero finalmente desarrolló shock séptico y megacolón tóxico, por lo que ingresó en la UMI 9 días después de que se originara el primer caso.

Por último, el sexto fue una mujer de 41 años que coincidió ingresada con los anteriores y que 27 días después del primer caso reingresó para una cirugía programada por cáncer de mama. Tras ser tratada en este último ingreso con ceftriaxona debutó con diarreas.

De todos los pacientes se recogieron muestras de heces que se enviaron al servicio de Microbiología. El algoritmo de diagnóstico en dicho laboratorio constaba de dos pasos. En primer lugar se detectaba la enzima glutamato deshidrogensa por inmunocromatografía (C.DIFF QUICK-CHECK, Techlab), y en segundo lugar, a los resultados positivos se les realizaba la detección de toxina B, toxina binaria y detección presuntiva del ribotipo 027 mediante PCR (GeneXpert, Cepheid). Todas las cepas de CDTR027 fueron confirmadas por el Hospital Universitario Gregorio Marañón.

En cuanto al tratamiento, este se realizó con vancomicina oral mayoritariamente y en los casos más graves con fidaxomicina. Dos de los pacientes, primer y quinto caso, fallecieron.

Viendo el transcurso de los acontecimientos, podemos afirmar con bastante certeza que el primer caso de CDTR027 fue importado desde Alemania, uno de los países europeos con mayor prevalencia de esta cepa [3].

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A pesar de que existen múltiples combinaciones en cuanto al algoritmo a seguir en el diagnóstico de *C. difficile* toxigénico y controversia entre los diferentes expertos [1,4,5], el algoritmo empleado en nuestro caso permitió detectar las cepas de CDTR027 de forma rápida. Esto, junto a las medidas adecuadas de aislamiento y vigilancia, evitó una gran diseminación hospitalaria del brote, quedando, a diferencia de otros hospitales [6], únicamente restringido a 6 casos. Además, como el sexto caso se produjo casi un mes después del primero, nos planteamos una vigilancia estrecha de aquellos pacientes que durante ese tiempo habían estado expuestos a las esporas y que podían actuar como portadores sanos.

A día de hoy seguimos empleando el mismo algoritmo diagnóstico y, aunque hemos tenido 4 nuevos episodios de CDTR027 en este tiempo, no se ha originado ningún nuevo brote. Pensamos que gracias a la rápida actuación de los profesionales sanitarios implicados, y sobre todo, a nuestro protocolo, que se caracteriza por un algoritmo en dos pasos y el diagnóstico molecular de *C. difficile* toxigénico que incluye la detección del ribotipo 027.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

REFERENCIAS

1. Rodríguez-Pardo D, Mirelis B, and Navarro F. Infecciones producidas por *Clostridium difficile*. Enferm Infeccy Microbiol Clin. 2013; 31(4): 254-263. DOI: 10.1016/j.eimc.2012.12.010
2. Asensio A, and Monge D. Epidemiología de la infección por *Clostridium difficile* en España. Enferm Infeccy Microbiol Clin, 2012; 30(6): 333-337. DOI: 10.1016/j.eimc.2011.09.010
3. Davies K. A, Ashwin H, Longshaw C. M, Burns D. A, Davis G. L, Wilcox M. H, et al. Diversity of Clostridium difficile PCR ribotypes in Europe: results from the European, multicentre, prospective, biannual, point-prevalence study of *Clostridium difficile* infection in hospitalised patients with diarrhoea (EUCLID), 2012 and 2013. Euro surveill. 2016; 21(29): 30294. DOI: 10.2807/1560-7917.ES.2016.21.29.30294
4. Crobach M. J. T, Planche T, Eckert C, Barbut F, Terveer E. M, Dekkers O. M, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2016; 22, S63-S81. DOI: 10.1016/j.cmi.2016.03.010 .
5. Kufelnicka A. M, & Kirn T. J. Effective utilization of evolving methods for the laboratory diagnosis of *Clostridium difficile* infection. Clin Infect Dis. 2011; *52*(12), 1451-1457. DOI: 10.1093/cid/cir201 .
6. Bouza E, Alcalá L, Marín M, Valerio M, Reigadas E, Munoz P, et al. An outbreak of Clostridium difficile PCR ribotype 027 in Spain: risk factors for recurrence and a novel treatment strategy. Eur J Clin Microbiol Infect Dis. 2017; 36(10), 1777-1786. DOI: 10.1007/s10096-017-2991-y

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Letter to the Editor

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Identification of *Anaerobiospirillum succiniciproducens* by MALDI-TOF mass spectrometer. A bacteremia in an immunocompetent patient

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Sir,

A 55-year-old man with a history of distal esophageal adenocarcinoma, treated with a minimally invasive esophagectomy, and a recently implanted DDD pacemaker due to persistent vasovagal syncopes presented to the emergency department with 72 hour-long febrile syndrome associated with mild odynophagia and dry cough. These symptoms were relatively controlled with the administration of paracetamol. In the complementary tests no alarming data or signs were observed, except a C-reactive protein of 29 mg/L, as well as a mild leukocytosis of 12,000 µl-1 with an 85% of neutrophils in the blood tests. Blood culture was obtained (2 extractions) and the patient was discharged home with antipyretic treatment.

The two anaerobic flasks of the blood culture were positive at 66 h and 67 h of incubation, with Gram stain showing curved Gram-negative rods. Given the morphology of the bacilli in the Gram stain, the sample was inoculated on BDTM Campy BAP, Brucella and MacConkey agars. Direct identification of the blood culture was conducted by MALDI-TOF mass spectrometer (Bruker, Massachusetts, USA) following the procedure proposed by Urrutikoetxea-Gutiérrez M *et al.* and *Anaerobiospirillum* spp. was obtained as identification with a value between 1.7 and 2.0 [1]. After the notification of this result the patient was admitted for completing the study and treated with intravenous imipenem (500 mg/6 h).

During the previous days he reported having presented inflammation, erythema and pain in the 4th finger of the left hand compatible with cellulitis. In addition, the patient stated that since the beginning of the year he has adopted a pet dog that has scratched him on one occasion and has had some episodes of diarrhea in the previous weeks.

After 48 h of incubation of the plates on anaerobic conditions, growth was observed only on Brucella agar as flat translucent colonies with negative catalase and oxidase reactions, confirming the identification of *A. succiniproducens* by MALDI-TOF MS with a value of 2,10. Identification was confirmed by 16S rRNA sequencing with *A. succiniproducens* as result with an homology percentage of 88,3%. Antibiotic susceptibility was performed by E-test on Brucella agar in anaerobiosis at 37ºC during 48h of incubation. Following the EUCAST (version 8.1, 2018) anaerobic Gram-negative rods and PK-PD cut-off points, the strain was susceptible to amoxicillin/clavulanate, cefuroxime, cefotaxime, imipenem, ertapenem, moxifloxacin and levofloxacin but resistant to penicillin, amoxicillin, clindamycin and metronidazole (Table 1).

A thoracoabdominal CT scan was performed, which ruled out infectious focus at those levels, as well as a transthoracic echocardiogram, which did not show data suggestive of endocarditis. After 72 h of admission, the patient evolved favorably and was discharged with 875 mg/125 mg of oral amoxicillin/clavulanate. However, due to an allergic reaction the antibiotic treatment had to be replaced to 400 mg/24 h of moxifloxacin, fulfilling 10 days of oral antibiotic treatment with good evolution.

The genus *Anaerobiospirillum* consists of only two species, *A. succiniproducens* and *Anaerobiospirillum thomasii*, which were both first isolated in 1967 from throat and animal stool samples [2]. *Anaerobiospirillum* spp. can be differentiated from other similar microorganisms such as *Campylobacter* spp. using classical microbiological techniques, being negative to the catalase and oxidase reactions and having a obligate anaerobic growth. Moreover, there are other structural differences such as lophotriche flagellation, an electron-dense ring located below the flagellated pole, or the existence of fibrillar structures that are oriented along the longitudinal axis that appear to be unique characteristics of this microorganism [4].

They are Gram-negative curved rods, which are part of the gastrointestinal commensal flora of cats and dogs and

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Table 1 **Susceptibility of the *A. succiniproducens* isolate**

Antibiotic	MIC (mg/L)	Interpretation
Penicillin	> 32	Resistant
Amoxicillin	16	Resistant
Amoxicillin/clavulanate	0.5	Susceptible
Cefuroxime	0.5	Susceptible
Cefotaxime	0.064	Susceptible
Imipenem	0.12	Susceptiblle
Ertapenem	0.012	Susceptible
Clindamycin	>32	Resistant
Metronidazole	>256	Resistant
Moxifloxacin	0.25	Susceptible
Levofloxacin	0.5	Susceptible

therefore having contact with animal faeces is probably one of the routes of transmission of infection in humans [3]. Another possible route of transmission could be the bite of colonized animals, as an *Anaerobiospirillum* bacteriemia after a cat bite has been previously described [5].

Around 50-60 human infections caused by *A. succiniproducens* have been described, being bacteremia or gastrointestinal infections the most frequent cases [6,7]. It has also been described as a cause of knee prosthesis infection [8]. Most infections occur in patients with comorbidities, ethylism or immunosuppression, however, as in the presented case it can also cause infection in immunocompetent patients [6-10]. Although the incidence of these infections is low, mortality is around 25-30% of cases, therefore, rapid action is essential [6,8].

For all these reasons, identification by MALDI-TOF mass spectrometry is a very important diagnostic tool, since it is a fast and accurate method that has been previously tested for the identification of *A. succiniciproducens* [6,7]. In addition, direct identification of the blood culture by MALDI-TOF makes the process even faster, being useful in the identification of potentially fatal and growth-demanding organisms such as *Capnocytophaga canimorsus* [11] While 16S ribosomal RNA gene sequencing is a more accurate method of identification, it is also more complicated, laborious and takes longer to arrive at identification. In fact, since Fox B *et al.* conducted their study in 2018 the Bruker MALDI-TOF database has been updated and includes now the main spectra of *A. succiniciproducens* [7].

The most appropriate antibiotic treatment of infections caused by *A. succiniproducens* remains to be determined due to limited experience. In the previous cases reported, this microorganism was sensitive to beta-lactams associated with beta-lactamase inhibitors, cephalosporins or chloramphenicol, showing variable sensitivity to penicillin and ampicillin [8]. It is usually resistant to anaerobicidal antibiotics such as metronidazole and clindamycin, as in our case. There are no specific fluoroquinolone cut-off points for anaerobic microorganisms, however, *A. succiniproducens* showed in vitro sensitivity to gemifloxacin and trovafloxacin in the article by Goldstein EJ et al. and, furthermore, in the manuscript by Kelesidis T, the patient was treated with satisfactory result with levofloxacin [12,13]. In our case, following EUCAST PK/PD cut-off points, both levofloxacin and moxifloxacin showed in vitro sensitivity. In fact, the patient received 10 days of oral treatment with moxifloxacin as sequential therapy after 72 h of intravenous treatment with imipenem without the appearance of complications, which adds further evidence to the possible in vivo activity of this microorganism.

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CONFLICT OF INTEREST

Authors declare have no conflict of interest

REFERENCES

1. Urrutikoetxea-Gutiérrez M, Sánchez Montiel M, Vidal-Garcia M, Basaras M, Cisterna Cancer R, Diaz de Tuesta Del Arco JL. Ultrafast direct method for identifying microorganisms from BACTEC lytic/10 anaerobic/F flasks. Future Microbiol. 2021;16:1381-1387. doi: 10.2217/fmb-2021-0059.

2. Davis, CP., Cleven D, Brown J, Balish E. Anaerobiospirillum, a new genus of spiral-shaped bacteria. Int J Syst Bacteriol. 1976;26(4), 498-504. Doi: 10.1099/00207713-26-4-498

3. Malnick H, Williams K, Phil-Ebosie J, Levy AS. Description of a medium for isolating Anaerobiospirillum spp., a possible cause of zoonotic disease, from diarrheal feces and blood of humans and use of the medium in a survey of human, canine, and feline feces. J Clin Microbiol. 1990 Jun;28(6):1380-4. doi: 10.1128/jcm.28.6.1380-1384.1990

4. Wecke J, Horbach I. Ultrastructural characterization of Anaerobiospirillum succiniciproducens and its differentiation from Campylobacter species. FEMS Microbiol Lett. 1999 Jan 1;170(1):83-8. doi: 10.1111/j.1574-6968.1999.tb13358.x.

5. Markusse IM, van Mens SP, de Vries PJ. An unusual causative pathogen of sepsis after a cat bite: Anaerobiospirillum succiniciproducens. Neth J Med. 2018 Mar;76(2):87-89. PMID: 29515010.

6. Alguacil-Guillen M, Ramos-Ruperto L, Ramos Ramos JC, Robles-Marhuenda A, García-Rodriguez J, Mingorance J, Romero-Gómez MP. MALDI-TOF MS for rapid diagnosis of Anaerobiospirillum succiniciproducens, an unusual causative agent of bacteraemia in

humans. Two case reports and literature review. Anaerobe. 2019 Feb;55:130-135. doi: 10.1016/j.anaerobe.2018.12.003.

7. Fox B, Berger MA, Roncallo M, Pinoche L, Ibáñez ME, Gonzalez-Fraga S, Fernández-Canigia L. MALDI-TOF MS in Anaerobiospirillum succiniciproducens bacteremia: A report of 4 cases in different hosts. Anaerobe. 2018 Dec;54:267-270. doi: 10.1016/j.anaerobe.2018.04.003.

8. Kelesidis T. Bloodstream infection with Anaerobiospirillum succiniciproducens: a potentially lethal infection. South Med J. 2011 Mar;104(3):205-14. doi: 10.1097/SMJ.0b013e318200c8d7.

9. Schaumburg F, Dieckmann R, Schmidt-Bräkling T, Becker K, Idelevich EA. First description of an Anaerobiospirillum succiniciproducens prosthetic joint infection. New Microbes New Infect. 2017 Mar 23;18:1-2. doi: 10.1016/j.nmni.2017.03.001.

10. Inokuchi R, Ishida T, Maeda J, Nakajima S, Yahagi N, Matsumoto A. Anaerobiospirillum succiniciproducens-induced bacteremia in a healthy man. Am J Emerg Med. 2014 Jul;32(7):812.e1-3. doi: 10.1016/j.ajem.2013.12.028.

11. Fernández Vecilla D, Calvo Muro FE, Renzi F, Díaz de Tuesta Del Arco JL. Sepsis caused by Capnocytophaga canimorsus in an immunocompetent patient. Rev Esp Quimioter. 2022;35(3):304-306. doi: 10.37201/req/006.2022.

12. Goldstein EJ, Citron DM, Vreni Merriam C, Tyrrell K, Warren Y. Activities of gemifloxacin (SB 265805, LB20304) compared to those of other oral antimicrobial agents against unusual anaerobes. Antimicrob Agents Chemother. 1999 Nov;43(11):2726-30. doi: 10.1128/AAC.43.11.2726.

13. Kelesidis T, Dien Bard J, Humphries R, Ward K, Lewinski MA, Uslan DZ. First report of treatment of Anaerobiospirillum succiniciproducens bloodstream infection with levofloxacin. J Clin Microbiol. 2010 May;48(5):1970-3. doi: 10.1128/JCM.02478-09.

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Letter to the Editor

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Response to "The importance of an early gastroenteritis diagnosis to discard MIS-C during SARS-CoV-2 pandemic"

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Sir,

We read the interesting paper by Fernández-Miaja et al. where they report four cases of *Campylobacter jejuni* infection in patients with an initial diagnostic suspicion of multiinflammatory syndrome in children (MIS-C) and highlight the importance of ruling out other potential diagnosis in order to avoid unnecessary diagnostic tests and treatment [1]. Interestingly, two of their cases showed marked lymphopenia (<1000/mm^3), one of them with associated elevated C-reactive protein values. American College of Rheumatology guidelines recommend a complete diagnostic evaluation to rule out MIS-C in children with unremitting fever, suggestive clinical features, elevated acute phase reactants and at least one among several laboratory features, including an absolute lymphocyte count below 1000/mm^3 in the absence of other causes that could explain the clinical picture [2]. One study in search of red flags that might help discriminate between MIS-C and other common febrile conditions in children, found that absolute lymphopenia and an elevated C-reactive protein serum concentration were associated with a higher risk of MIS-C [3].

Does *Campylobacter* infection alone explain the association of fever, elevated C-reactive protein values and absolute lymphopenia? Can a child with these findings be safely sent home if a *Campylobacter* PCR test is positive or might a short period of observation in the hospital still be advisable?

We reviewed the clinical files of 110 children younger than 14 years of age with a diagnosis of *Campylobacter* infection seen in our hospital from January 1st2017 to June 1st2022 and compared the frequency of cases showing both elevated C-reactive protein and lymphopenia before (up to January 2020) and after the start of SARS-CoV-2 pandemia (from January 2020 onwards).

Results are shown in Table 1. As expected, more cases of *Campylobacter* infection were diagnosed in the first period while more laboratory studies were performed in the second period (47.2% vs 14.9%), probably as a reflection of the fear of missing a possible diagnosis of MIS-C in the pandemic era. No cases showing both elevated C-reactive protein and profound lymphopenia were observed among the 74 children seen in the prepandemic period, while four (11.1% of the total cases and 30.6% of those in whom laboratory tests were performed) were found in the pandemic era. Evidence of SARS-CoV-2 exposure in the previous weeks was confirmed in three of these cases and infection was documented in one child, who was initially diagnosed as possible MIS-C and treated with intravenous gammaglobulin and corticosteroids for one day; treatment was suspended when the diagnosis of *Campylobacter* infection was confirmed. Clinical characteristics and laboratory findings of these four patients are shown in table 2.

Our results raise the question of whether *Campylobacter* infection alone can be accountable for these laboratory findings and if a positive stool test can safely rule out a diagnosis of MIS-C or a short observation period in the hospital would be prudent, as children with MIS-C may develop additional organ system involvement over the course of admission [4]. Lymphopenia has been previously described in up to 11% of patients with *Campylobacter* infection returning from the tropics,

Table 1 Comparison between the two periods.

Time interval	*Campylobacter* infection cases	Positive study*	Negative study	No studies performed
2017-2019	74	0	11	63
2020-2022	36	4	13	19

*Positive study: C-reactive protein >30 mg/L AND absolute lymphocye count <1000/mm^3

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Table 2 **Patient characteristics and laboratory findings of the four patients with fever, lymphopenia and elevated acute phase reactants associated with *Campylobacter* infection.**

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Demographic				
Sex	Female	Female	Male	Female
Patient age (years)	8	9	12	11
SARS-CoV-2				
Exposure	No	Yes (1 month earlier)	Yes (3 weeks earlier)	Yes (3 months earlier)
Infection	No	No	Yes (2 weeks earlier)	No
Presenting symptoms				
Days of fever at presentation	2	1	1	3
Abdominal pain	Yes	Yes	Yes	Yes
Vomiting	Yes	Yes	No	No
Diarrhea	Yes	No	Yes	Yes
Generalized myalgia	No	No	Yes	Yes
Laboratory values				
WBC/ml	6360	7780	11800	8960
Neutrophils/ml	5400	5930	9959	7350
Lymphocytes/ml	680	920	800	970
Hemoglobin (g/dl)	13,5	13,4	13,2	12,6
Platelets/ml	281000	108000	191000	228000
C-Reactive Protein (mg/L)	97	208	116	36
Procalcitonin (ng/ml)	ND	1,27	1,24	ND
SARS-CoV-2 RT PCR	Negative	Negative	Negative	Negative
Stool culture	*Campylobacter jejuni*	*Campbylobacter jejuni*	*Campylobacter jejuni and Yersinia enterocolitica*	*Campylobacter jejuni*
Disposal and Treatment				
Disposal	Admission (Surgery)	Admission Pediatric Intensive Care Unit	Admission Pediatric Ward	Discharged Home
Treatment	Appendicectomy Azithromycin	Azithromycin	Corticosteroids and intravenous gammaglobulin (1 day); azithromycin	None

RT-PCR: Reverse transcription polymerase chain reaction. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. WBC: White blood cells.

but higher cut-off points to define lymphopenia were used in that study [5]. In a previous series of five cases of bacterial enteritis (4 *Salmonella* species, one *Campylobacter* species) mimicking MIS-C [4], although four patients had mild lymphopenia, none had an absolute count less than 1000 lymphocytes/mm^3.

Our study has several limitations, including the small number of cases, its retrospective nature, the low frequency of laboratory tests in the prepandemic period, the lack of data on SARS-CoV-2 infection in most of our patients, and the lack of serologic studies regarding their SARS-CoV-2 status, and larger prospective studies may shed light upon this subject.

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Authors declare have no conflict of interest

REFERENCES

1. Fernández-Miaja M, Vivanco-Allende A, Delgado-Nicolás, S, Llaneza-Velasco ME, Fernández-Domínguez J. The importance of an early gastroenteritis diagnosis to discard MIS-C during SARS-CoV-2 pandemic. Rev Esp Quimioter 2022;35(4):406-7. DOI: 10.37201/req/170.2021
2. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children associated with SARS-CoV-2 and hyperinflammation in pediatric Covid-19: Version 3. Arthritis Rheumatol. 2022 Apr;74(4):e-e20. DOI: 10,1002/art.42062.Epub 2022 Feb 3.
3. Carlin RF, Fischer AM, Pitkowsky Z, Abel D, Sewell TB, Landau EG, et al. Discriminating Multisystem Inflammatory Syndrome in children requiring treatment from common febrile conditions in outpatient settings. J Pediatr 2021;229:26-32. DOI: 10.1016/j.jpeds.2020.10.013.
4. Dworsky ZD, Roberts JE, Son, MBF, Tremoulet AH, Newburger JW, Burns JC. Mistaken MIS-C: a case series of bacterial enteritis mimicking MIS-C. Pediatr Infect Dis J 2021;40 (4):e159-e161. DOI: 10.1097/INF.0000000000003050.
5. Herbinger KH, Hanus I, Beissner M, Berens-Riba N, Kroidl I, von Sonnenburg F, et al. Lymphocytosis and lymphopenia induced by imported infectious diseases: a controlled cross-sectional study of 17,229 diseased German travelers returning from the Tropics and Subtropics. Am J Trop Med Hyg 2016;94(6):1385-91. DOI:10.4269/ajtmh.15-0920.

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Letter to the Editor

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Periprosthetic joint infection caused by *Haemophilus parainfluenzae*. Case report and literature review

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Sir,

Haemophilus parainfluenzae is a pathogen that has been implicated in a broad spectrum of infectious diseases. It is a small, pleomorphic, Gram-negative coccobacillus with fastidious growth requirements mostly found as a commensal bacterium in human upper respiratory tract and oral cavity [1]. It can also be isolated from other mucosal surfaces such as the gut, urethra and vagina [2]. It often causes respiratory and musculoskeletal infections in immunocompromised patients but is not commonly found in osteoarticular infections [2–5].

Moreover, periprosthetic joint infection (PJI) is a disastrous complication that occurs in 1% to 2% of primary and in 4% of revision arthroplasties. In addition, PJI can complicate up to 20% of revision arthroplasties. Most of these infections are caused by Gram-positive microorganisms, where *the Staphylococcus* genus tops the list, and with *Staphylococcus aureus* and *S. epidermidis* being the leaders [6].

In this clinical case we present an infection of a left total knee prosthesis by this extremely unusual bacterium in an immunocompetent patient caused by this microorganism. This study was approved by the ERC of the institution (reference EO053-21_FJD).

The patient was a 67-year-old man with a personal history of hypertension and diabetes mellitus type 2. He was attended in 2009 because pain and blockages of the left knee joint, which seems to have been resolved after 6 months by treatment with chondrosulphuric acid infiltration. In 2015 he again reported pain in his left knee, and again underwent infiltration without success, so in May 2016 it was decided to perform a cemented total knee arthroplasty.

A year later, in May 2017, he came back again because of progressive pain, and a possible loosening of the prosthesis was observed on radiographs. C-reactive protein (CRP) was 3 mg/dL and erythrocyte sedimentation rate (ESR) of 42 mm/h in addition to abundant joint effusion. An arthrocentesis for culture and study of the joint fluid was performed. Cell count was 6,280 cells/mm3 (85% polymorphonuclears), with glucose 177.0 mg/dl and CRP 6.84 mg/dl. This sample was inoculated in the following culture media: Tryptic soy sheep blood agar (TSS), chocolate agar (CHA), Shaedler-5% sheep blood agar (SCS), MacConkey agar (McC), and part of the fluid was also inoculated in a blood culture bottle (BactAlert), all from Biomérieux Marcy l'Etoile, France). TSS, CHA and McC were incubated at 37ºC in a 5% CO_2 atmosphere. SCS was incubated in an anaerobic atmosphere at 37ºC. All media were incubated for 15 days.

Following these results, a revision surgery was performed in October 2017. During the surgery, the 9 samples were obtained: 1 from histopathology, and 8 for culture: 4 periprosthetic tissue biopsies, 3 components of the prosthesis and 1 synovial fluid.

Histopathology of the biopsy showed no polymorphonuclear cells; only hyperplasia of synoviocytes was observed together with hyalinized tissue. A one-stage revision, using a rotational hinge was performed (Figure 1).

One month later, the patient came to the emergency room with progressive pain and swelling in the right knee and a fever of 38.8 ºC. The X-ray of the right knee showed no loosening and a white blood cell count of 12,000 cells/mL with 83% PMN cells, and a CRP of 1.3 mg/liter. At the same time, it was decided to perform a second arthrocentesis to extract the joint fluid and proceed to its analysis and microbiological culture. This analysis showed a blood fluid count of 35,850 leukocytes/mL (92% polymorphonuclear) and 38,0000 red blood cells/mL. In addition, this liquid was inoculated in a blood culture bottle and incubated at 37 ºC, being positive after 19.7 hours incubation. A subculture was performed in the usual media for bac-

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Figure 1A

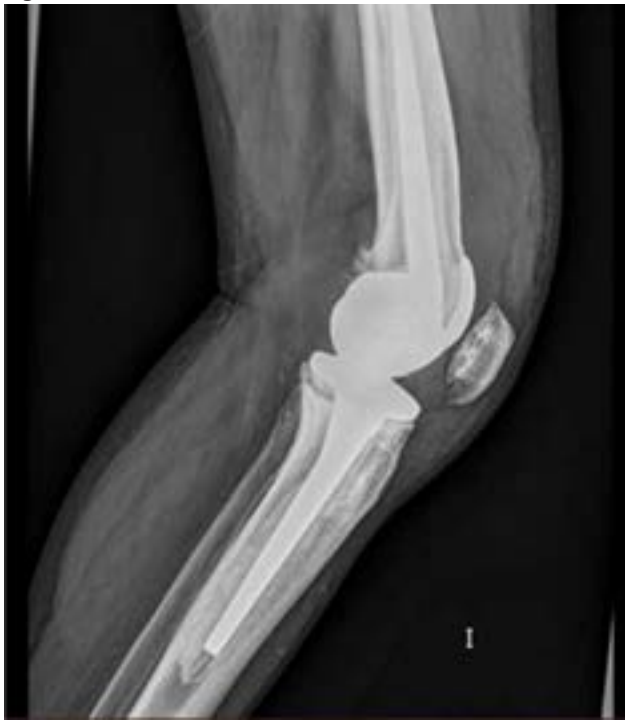

Figure 1B

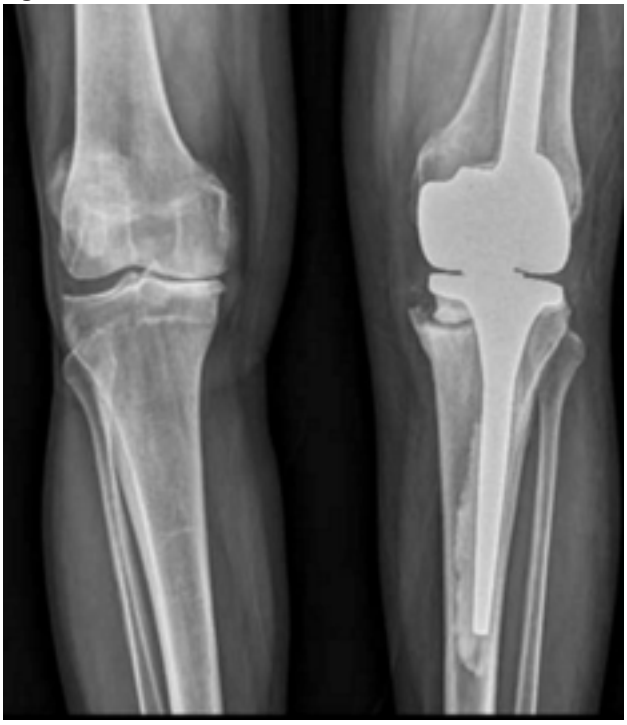

Figure 1 | **Knee X-rays: frontal view of the left and right knees (Figure 1A), lateral view of the left knee (Figure 1B).**

teria and, after 24 h of incubation, growth of small translucent colonies was observed in the chocolate agar. They were identified as *Haemophilus parainfluenzae* colonies by MALDI-TOF technique (VitekMS, BioMérieux, Marcy l'Etoile, France). Its susceptibility was tested by disc diffusion technique according to EUCAST criteria (*Haemophilus* test medium: 35ºC ± 2ºC in 5% CO_2 for 16–18 hours), so our microorganism showed susceptibility to ciprofloxacin, chloramphenicol, tetracycline, cefuroxime, amoxicillin-clavulanic acid, ceftriaxone, cotrimoxazole and meropenem, being resistant to ampicillin and clarithromycin. Subsequently, a debridement, antibiotics and implant retention (DAIR) procedure was performed including polyethylene replacement. Several samples were collected for microbiological culture: joint fluid, polyethylene and 5 tissue samples.

All tissue samples were inoculated in TSS, CHA, SCS, McC and Sabouraud chloramphenicol agar slants (SC). The joint fluid was inoculated in TSS, CHA, McC and SCS. Polyethylene sample was sonicated according to the previously described protocol [7]. All media were incubated for 15 days.

After 2 days of incubation, small colonies were detected in 2 of 5 tissue samples and the joint fluid. Finally, *H. parainfluenzae* was identified again with the same antibiotic susceptibility. The patient was treated with ceftriaxone 2 g/24 h and ciprofloxacin 400 mg/12 h intravenously for 7 days and then was switched to ciprofloxacin 500 mg/12 h and cotrimoxazole 800/160 mg/8 h orally for a total of 6 months. The patient gradually improved, with a decrease in CRP in blood tests (1.55 mg/dl 1 month after surgery) and the other inflammatory markers, in addition to and improvement in his mobility. Finally, the patient was considered cured after 3 years of follow-up.

This microorganism is part of the normal microbiota of the mouth and upper respiratory tract, and it can be responsible for a broad spectrum of serious infections such as endocarditis, bacteremia, and pneumonia [8]. However, PJI due to *H. parainfluenzae* is an extremely rare entity, with only 4 case patients reported in the medical literature, 3 of them occurred after procedures in the oral cavity (Table 1) [2–5].

In most cases, *H. parainfluenzae* infection is usually preceded by an invasive procedure, including those in the oral cavity [1,3–5,8]. In our case, the age of our patient (67 years) is very close to the average age of the cases already published in the literature (76 years) [9]. He also has a history of diagnosed diabetes mellitus type II hypertension, a septoplasty performed in 2006 and a radical prostatectomy performed in 2012. A few months before the first left total knee replacement, he also underwent a successful shoulder operation.

The source of our patient's infection is unclear, but we can contemplate the possibility that it was this shoulder surgery the patient underwent due to the proximity between this extremity and the respiratory tract. In addition, like other cases

Table 1 **Cases of prosthetic *H. parainfluenzae* infection reported in the literature**

	Age/sex	Prosthetic joint	Comorbidities	Positive samples	Surgical intervention	Therapy	Length of therapy	Outcome
Present case	67 / M	TKP	Type 2 DM Hypertension Shoulder operation Left knee arthroplasty	Joint fluid Two periprosthetic tissue	DAIR. Replacement of polyethylene.	Ceftriaxone 2 g/24 h and ciprofloxacin 400 mg/12 h IV (7 days) → oral ciprofloxacin 500 mg/12 h and oral cotrimoxazole 800/160 mg/8 h	6 months	Cure
Jellicoe et al. [3]	78 / F	THP	Arthroplasty complication Dental extraction	Joint fluid	Two-stage replacement	After washout: Gentamicin beads and cement spacer Flucloxacillin/ ampicillin (500/500 mg)	10 months	Cure
Manian et al. [4]	72 / M	TKP	Root-canal procedure	Joint drainage	Surgery refused	Oral cephalexin (6 months) → IV ceftriaxone (2 months) → oral ciprofloxacin	> 2 years	Chronic infection
Pravda et al. [5]	78 / F	TKP	Arthroplasty complication Root-canal procedure	Joint fluid	Arthroscopic irrigation and debridement	IV ampicillin (1 month) → oral amoxicillin (2 months)	3 months	Cure
Bailey et al. [2]	75 / M	TKP	Chronic lymphoid leukemia Arthroplasty complication	Joint fluid One peripros-thetic tissue	two-stage replacement	Only flucloxacillin and rifampicin (6 weeks) without success (before surgery) → cement spacer with 1g of gentamicin and 2g of vancomycin (after first stage) → 3 dosis of oral cefuroxime (750 mg)	No reported	Cure

DAIR: Debridement, antibiotics, and implant retention; DM: Diabetes mellitus; F: female, IV: intravenous, M: male; THP: total hip prosthesis; TKP: total knee prosthesis.

published in the literature with an extended asymptomatic period between surgery and the onset of symptoms, it establishes the hematogenous route as the most likely cause of infection. [3,4,10–12].

Antibiotic resistance in this organism is more diverse and widespread than is commonly appreciated. It may show resistance to penicillins such as ampicillin and amoxicillin, including amoxicillin-clavulanic acid and some cephalosporins due to the presence of beta-lactamases. They remain in most cases susceptible to carbapenems and quinolones, while the rate of resistance to clarithromycin in Spain exceeds 22.5% [9,13,14]. In our case, *H. parainfluenzae* was resistant to clarithromycin and ampicillin, remaining susceptible to the other antibiotics tested. Our patient was successfully cured after intravenous treatment with a cephalosporin followed by de-escalation to oral cotrimoxazole and ciprofloxacin for 6 months. In most of the cases described this is the time and treatment indicated, but it can be as long as 2 years [4,14,15].

In summary, despite the high prevalence of *H. parainfluenzae* in the normal oral microbiota, its low pathogenic power makes it a very rare microorganism in this pathology. To our knowledge, only 4 cases of PJI with this bacterium have been reported. In addition, most PJI are due to Gram-positive microorganisms such as coagulase-negative *staphylococci* and *S. aureus*, as well as some Gram-negative bacilli, such as *Escherichia coli*, while *H. parainfluenzae* is a very rare microorganism. Therefore, correct and early microbiological diagnosis is essential for a good outcome of these infections.

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CONFLICT OF INTEREST

Authors declare have no conflict of interest

REFERENCES

1. Onafowokan OO, Mateo R, Bonatti HJR. A Series of *Haemophilus parainfluenzae* Surgical Infections and Review of the Literature. Surg Infect (Larchmt). 2021;22(9):940-947. doi: 10.1089/sur.2020.172
2. Bailey C, Duckett S, Davies S, Townsend R, Stockley I. *Haemophilus parainfluenzae* prosthetic joint infection. The importance of accurate microbiological diagnosis and options for management. J Infect. 2011;63(6):474-6. doi: 10.1016/j.jinf.2011.08.009
3. Jellicoe PA, Cohen A, Campbell P. *Haemophilus parainfluenzae* complicating total hip arthroplasty: A rapid failure. J Arthroplasty. 2002;17(1):114-6. doi: 10.1054/arth.2002.29314
4. Manian FA. Prosthetic joint infection due to Haemophilus parainfluenzae after dental surgery. South Med J. 1991;84(6):807-8. doi: 10.1097/00007611-199106000-000
5. Pravda J, Habermann E. Hemophilus parainfluenzae complicating total knee arthroplasty. A case report. Clin Orthop Relat Res. 1989;(243):169-71.
6. Gallo J, Nieslanikova E. Prevention of Prosthetic Joint Infection: From Traditional Approaches towards Quality Improvement and Data Mining. J Clin Med. 202011;9(7):2190. doi: 10.3390/jcm9072190.
7. Esteban J, Gomez-Barrena E, Cordero J, Martín-de-Hijas NZ, Kinnari TJ, Fernandez-Roblas R. Evaluation of Quantitative Analysis of Cultures from Sonicated Retrieved Orthopedic Implants in Diagnosis of Orthopedic Infection. J J Clin Microbiol. 2008;46(2):488-92. doi: 10.1128/JCM.01762-07
8. Cobo F, Jiménez G, Rodríguez-Granger J, Sampedro A, Aliaga-Martínez L. A Rare Case of Osteomyelitis Caused by Haemophilus Parainfluenzae. J Bone Jt Infect. 2017;2(2):104-106. doi: 10.7150/jbji.17387. eCollection 2017
9. O'Neil CR, Wilson E, Missaghi B. Bone and Joint Infections due to Haemophilus parainfluenzae: Case Report and Review of the Literature. Can J Infect Dis Med Microbiol. 2016;2016:4503025. doi: 10.1155/2016/4503025
10. Danilkowicz RM, Lachiewicz AM, Lorenzana DJ, Barton KD, Lachiewicz PF. Prosthetic Joint Infection After Dental Work: Is the Correct Prophylaxis Being Prescribed? A Systematic Review. Arthroplast Today. 2021 Jan 9;7:69-75. doi: 10.1016/j.artd.2020.11.007.
11. Fitzgerald RH, Nolan DR, Ilstrup DM, Van Scoy RE, Washington JA, Coventry MB. Deep wound sepsis following total hip arthroplasty. J Bone Joint Surg Am. 1977 Oct;59(7):847-55.
12. Stinchfield FE, Bigliani LU, Neu HC, Goss TP, Foster CR. Late hematogenous infection of total joint replacement. J Bone Joint Surg Am. 1980;62(8):1345-50.
13. Soriano F, Granizo JJ, Coronel P, Gimeno M, Ródenas E, Gracia M, et al. Antimicrobial susceptibility of *Haemophilus influenzae, Haemophilus parainfluenzae* and *Moraxella catarrhalis* isolated from adult patients with respiratory tract infections in four southern European countries. Int J Antimicrob Agents. 2004;23(3):296-9. doi: 10.1016/j.ijantimicag.2003.07.018.
14. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial Resistance in Haemophilus influenzae. Clin Microbiol Rev. 2007;20(2):368-89. doi: 10.1128/CMR.00040-06.
15. Cobo F, Jiménez G, Rodríguez-Granger J, Sampedro A, Aliaga-Martínez L, Navarro-Marí JM. Clinical and microbiological findings of septic arthritis caused by Haemophilus parainfluenzae. Med Mal Infect. 2017;47(8):526-531. doi: 10.1016/j.medmal.2017.08.002.

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Letter to the Editor

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Bacteremia caused by *Eikenella corrodens* in a patient with pelvic inflammatory disease

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Sir,

Eikenella corrodens is a HACEK group microorganism belonging to the *Neisseriaceae* family. This slow-growing bacteria is a facultative anaerobic, non-motile Gram-negative rod, that is part of of human oropharyngeal and genitourinary microbiomes. However, the pathogenicity of the species has not to be overlooked as *E. corrodens* is one of the mayor actors driving the periodontal disease and other severe infections. The species was named after the ability to corrode the agar that up to 50% present [1]. Colonies have a characteristic bleach-like odor and might occasionally present a light alpha-hemolysis. In this manuscript, we present a bacteremia caused by *E. corrodens* in a patient with pelvic inflammatory disease.

A 49-year-old woman attended the emergency department with a 72-hour febrile syndrome associated with abdominal pain and hyperemesis. The physical examination located the pain on the left flank and the Blumberg's sign was positive. The Blood tests presented an elevated C-reactive protein (24 mg/dL) and a discrete leukocytosis (18,600 leukocytes μl^{-1} with 91% neutrophils). The patient had an intrauterine device (IUD) and the transvaginal ultrasound was showed a trabeculated elongated image of 76 x 35 mm with diffuse echoes inside, compatible with a pyosalpinx in the left adnexal area, as well as a heterogeneous image of 81 x 60 mm compatible with a tuboovarian abscess in the right adnexal area. Computed tomography (CT) (Figure 1) confirmed the ultrasound findings, so the patient was admitted to the gynecological ward. Vaginal and endocervical samples were obtained, and IV therapy with 4 g/500 mg of piperacillin-tazobactam every 8h was initiated.

After 48 hours and due to the persistence of fever and the torpid evolution blood cultures were obtained and a subtotal hysterectomy and double laparotomic adnexectomy was performed. During the surgery, adhesions of intestinal loops to the uterine fundus and bladder plica were found, as well as bilateral tuboovarian abscesses of approximately 7 cm each (the right one adhered to the posterior uterine face and the left one adhered to the Douglas pouch fundus. Intraoperatory samples were taken from one of the abscesses and sent to the microbiology laboratory for microbiological identification.

The intraoperatory sample was inoculated on chocolate, TSA with 5% sheep blood, CNA, McConkey and Brucella agars, as well as on Thioglycollate enrichment broth. However, after 7 days of incubation, no growth was observed. The blood culture was positive after 5 days of incubation and Gram staining showed Gram-negative bacilli andit was subcultured on chocolate, TSA with 5% of sheep blood and McConkey agars in aerobiosis with 5% of CO_2. After 48-72h a subtle growth of pale yellow colonies on TSA and chocolate agars (Figure 2) was observed. These colonies were embedded in the agar, had a distinct hypochlorite odor and were oxidase positive and catalase negative. The BD Phoenix^R system was not able to identify the bacterial species and therefore 16S rRNA gene sequencing was performed directly from the blood culture, obtaining a sequence that aligned with *E. corrodens* with a homology percentage of 99.37%. The sequence was registered in GenBank with accession number OP679804. The susceptibility of the strain was studied using gradient strips on fastidious Muller-Hinton agar, resulting susceptible to fluoroquinolones and all beta-lactams but ampicillin, as well as resistant to clindamycin.

After one week of IV antibiotic therapy and given the good clinical evolution, the treatment was sequenced to oral therapy with 875 mg/125 mg/8 hours of amoxicillin-clavulanic acid, fulfilling 2 weeks of antibiotic treatment in total.

Periodontitis and opportunistic infections are frequently caused by *E. corrodens*, with a tendency to cause abscesses in very variate locations , but most frequently on the head and neck [1-3]. Although normally most infections are benign

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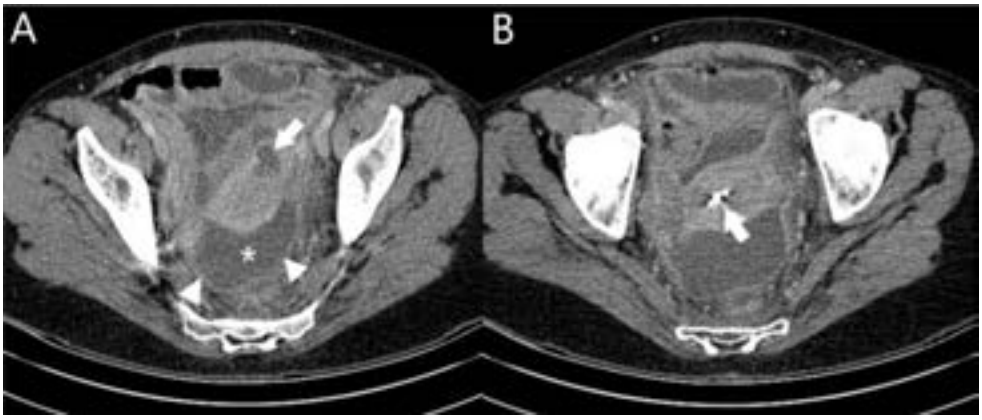

Figure 1 | **A) Axial slice of a pelvic CT after IV contrast that shows fluid (asterisk), peritoneal enhancement (arrowhead) and a tuboovarian abscess on the left (arrow). B) Lower slice shows IUD (arrow).**

Figure 2 | **Slow growth of pale yellow colonies on TSA and chocolate agars was observed after 48 h/72h of incubation. Identification was confirmed by 16S rRNA sequencing as *Eikenella corrodens* with an homology percentage of 99.37%.**

and indolent, invasive and recurrent infections, such perirenal abscesses, vertebral osteomyelitis or endocarditis have been reported; [4-6]. Gynaecological infections such as chorioamnionitis or tubo-ovarian abscesses caused by *E. corrodens* are rare, but these have been described mostly in women using IUD [7-9].

This fastidious, slow-growing bacteria frequently causes polymicrobial infections and may be underdiagnosed as it is frequently outgrown by coinfecting microorganisms in standard culture media [2,9]. On the other hand, *E. corrondens* can grow exponentially when *Streptotoccus spp.* of various strains are present [10]. Before the appearance of MALDI-TOF mass spectrometer, the identification of *E. corrodens* was performed according to the type of growth on agars and through biochemical tests or 16S rARN sequencing, extending the identification time. MALDI-TOF MS represents an accurate, rapid and inexpensive tool for the detection of slow-growing and fastidious pathogen. Its utility in the identification of microorganisms from the HACEK group has been proved previously with good results [11].

It is vital to emphasize the importance of taking microbiological samples before starting antibiotic treatment to not to delay diagnosis. Even more so when the infection is caused by a microorganism with a demanding growth such as *E. corrodens*, whose identification was a laborious process before the appearance of the MALDI-TOF mass spectrometer. In the present case, the clinical situation did not allow to delay the antimicrobial therapy until the drainage of the collections, however, blood cultures should have been extracted upon arrival at the emergency department.

E. corrodens is usually susceptible to beta-lactams, fluoroquinolones and tetracyclines. Some strains can produce β-lactamases, whereas all strains are intrinsically resistant to clindamycin and metronidazole [12,13]. In addition, *E. corrodens* present low rates of *in vitro* susceptibility to to erythromycin and aminoglycosides. However, despite appropriate

antimicrobial therapy, infections caused by this microorganism are prone to relapse, especially when the duration of the antimicrobial therapy is insufficient or the collections are not drained [14]. Early control of the focus in these infections is essential to avoid serious complications such as bacteremia or septic shock. However, in the presented however a conservative approach was decided and the surgery was postponed 24/48 h, hoping that the intravenous therapy could stabilize the patient.

E. corrodens is a commensal of the human body, but when translocated to other anatomical sites it cause severe infections. Therefore, it is very important to correctly isolate this microorganism and know its role in gynaecological infections to achieve a proper treatment.

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CONFLICT OF INTEREST

Authors declare have no conflict of interest

REFERENCES

1. Li L, Shi Y B, Weng X B. *Eikenella corrodens* infections in human: Reports of six cases and review of literatures. J Clin Lab Anal 2022, 36 (2), e24230. DOI: 10.1002/jcla.24230
2. Rodríguez-Rojas L, Suarez-López A, Cantón R, Ruiz-Garbajosa, P. *Eikenella corrodens* causing deep-seated infections. Six-year experience in a University Hospital in Madrid. Enferm Infecc Microbiol Clin (Engl Ed) 2020, 38 (2), 76-78. DOI: 10.1016/j.eimc.2019.04.004
3. Chen C K, Wilson M E. *Eikenella corrodens i*n human oral and non-oral infections: a review. J Periodontol 1992, 63 (12), 941-953. DOI: 10.1902/jop.1992.63.12.941
4. Dhaese S, De Wilde V, Snauwaert C, Orlent H. *Eikenella corrodens* perirenal abscess resulting from a pancreatic fistula in a patient with chronic pancreatitis. Case report and literature review. Acta Gastroenterol Belg 2018, 81 (2), 323-326.
5. Ranabhat K, Bhatta S, Bhatta R K, Acharya Y. *Eikenella Corrodens* Vertebral Osteomyelitis in a Young Patient With Type I Diabetes Mellitus. Cureus 2020, 12 (8), e9553. DOI: 10.7759/cureus.9553
6. Sharara S L, Tayyar R, Kanafani, ZA, Kanj SS. HACEK endocarditis: a review. Expert Rev Anti Infect Ther 2016, 14 (6), 539-545. DOI: 10.1080/14787210.2016.1184085
7. Correa Martínez L, González Velasco C, Gaona Álvarez CE, Sánchez Castañón J. Tuboovarian abscess due to *Eikenella corrodens*. Enferm Infecc Microbiol Clin (Engl Ed). 2018 May;36(5):319-320. doi: 10.1016/j.eimc.2017.09.009.
8. Angulo López I, Aguirre Quiñonero A, Fernández Torres M, Alegría Echauri E. Chorioamnionitis and neonatal septicaemia due to *Eikenella corrodens*. Enferm Infecc Microbiol Clin. 2017 Apr;35(4):266-267. doi: 10.1016/j.eimc.2016.03.004.
9. Drouet E, De Montclos H, Boude M, Denoyel, G A. *Eikenella corrodens* and intrauterine contraceptive device. Lancet. 1987;2(8567):1089. doi: 10.1016/s0140-6736(87)91517-0.
10. Young K A, Allaker R P, Hardie J M, Whiley R A. Interactions between *Eikenella corrodens* and '*Streptococcus milleri*-group' organisms: possible mechanisms of pathogenicity in mixed infections. Antonie Van Leeuwenhoek 1996, 69 (4), 371-373. DOI: 10.1007/BF00399626.
11. Couturier MR, Mehinovic E, Croft AC, Fisher MA. Identification of HACEK clinical isolates by matrix-assisted laser desorption ionization-time of flight mass spectrometry. J Clin Microbiol. 2011;49(3):1104-6. doi: 10.1128/JCM.01777-10.
12. Goldstein E J, Citron D M, Merriam C V, Warren Y A, Tyrrell K L, Fernandez, H. In vitro activities of a new des-fluoroquinolone, BMS 284756, and seven other antimicrobial agents against 151 isolates of *Eikenella corrodens*. Antimicrob Agents Chemother 2002, 46 (4), 1141-1143. DOI: 10.1128/AAC.46.4.1141-1143.2002.
13. Lacroix J M, Walker C. Characterization of a beta-lactamase found in *Eikenella corrodens*. Antimicrob Agents Chemother 1991, *35* (5), 886-891. DOI: 10.1128/AAC.35.5.886.
14. Sheng W S, Hsueh P R, Hung C C, Teng L J, Chen Y C, Luh K T. Clinical features of patients with invasive *Eikenella corrodens* infections and microbiological characteristics of the causative isolates. Eur J Clin Microbiol Infect Dis 2001, 20 (4), 231-236. DOI: 10.1007/pl00011259.

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Carta al Director

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Otomastoiditis tuberculosa: a propósito de un caso

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En los últimos años se ha observado un incremento de casos de tuberculosis (TBC) a nivel mundial debido a factores de riesgo; siendo los principales: portador del Virus de Inmunodeficiencia Humana, inmigrantes, hacinamiento, abuso de sustancias y pacientes en tratamiento con terapia biológica. El 25% de las TBC son de presentación extrapulmonar [1] y establecer su diagnóstico es un reto y requiere un elevado índice de sospecha.

A continuación, presentamos un caso de otomastoiditis tuberculosa (OT) en un paciente inmunocompetente: varón de 49 años, fumador e hipertenso, consumidor de cocaína por vía nasal y anfetaminas. Acudió a su médico de atención primaria por sensación de taponamiento y sordera de un mes de evolución. En la otoscopia se observó una pequeña perforación central anterior y posterior timpánica. Se recogió cultivo aislándose *Enterobacter cloacae* sensible a ciprofloxacino con el que fue tratado (2g c/12h) durante 10 días. Tres meses después acudió por empeoramiento de los síntomas. Se realizó un TAC craneal donde se observó cambios crónicos compatibles con una otitis media crónica (OMC) no colesteatomatosa con ocupación de ambas mastoides con moco, pus y con hipertrofia mucosa de la caja en región atical. Se aplicó polvo boricado y se alternó ciprofloxacino y ciclopirox.

Tras 7 meses, el oído derecho presentaba otorrea lechosa y el oído izquierdo se encontraba seco, pero el mango del martillo descubierto. Se realizó una audiometría tonal liminal presentando una hipoacusia de trasmisión bilateral, con un gap de 70 dB en el oído izquierdo y >40 dB en odio derecho, con gran afectación de la inteligibilidad. La impresión diagnostica fue de una OMC no colesteatomatosa con afectación de la audición, en la que se planteó tratamiento quirúrgico.

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Cuatro semanas después presentó malestar general, astenia y pérdida de peso. Tras la exploración física se realizó un TAC torácico observándose hallazgos compatibles con afectación pulmonar por tuberculosis, y un TAC craneal en el que se observaron signos de otomastoiditis aguda sin erosiones en oído medio e interno y celdillas mastoideas con secreciones (Figura 1). La tinción de Ziehl Neelsen en esputo fue positiva, y la PCR para la detección de *M. tuberculosis* mediante Xpert MTB/RIF® en muestras respiratorias y óticas fueron positivas. La PCR de estas mismas muestras mediante Xpert XDR® evidenció la ausencia de resistencia a los tuberculostáticos testados (isoniazida, fluoroquinolonas, amikacina, kanamicina, capreomicina y etionamida). En el cultivo de micobacterias se aisló *M. tuberculosis* en ambas muestras. Se estudió la sensibilidad antibiótica mediante el Sistema BD BACTEC™ MGIT™ siendo sensible a estreptomicina, isoniacida, rifampicina, etambutol y pirazinamida.

La determinación del interferón gamma mediante QuantiFERON®-TB Gold fue positiva, las serologías de Lues, VHB, VHC, y VIH fueron negativas. Fue diagnosticado de tuberculosis pulmonar bacilífera y OT. Se inició tratamiento dirigido.

La OT es una causa poco frecuente de OMC supurativa y se observa con mayor frecuencia en adultos inmunodeprimidos. Los hallazgos en la OT son inespecíficos y la fiebre es infrecuente, la triada clínica característica es: otorrea purulenta indolora, perforación timpánica múltiple (más frecuente pero no patognomónica), y parálisis facial [2]. Nuestro paciente presentó otorrea y perforación timpánica. Ya que la coexistencia de todos los síntomas es rara, la OT es difícil de diagnosticar, y debería ser considerada en el diagnóstico diferencial de la OMC ante una otorrea crónica que no mejora con tratamiento médico habitual. La patogénesis de la OT implica, fundamentalmente, tres mecanismos posibles: a) aspiración de moco a través de la trompa de Eustaquio desde la nasofaringe, b) diseminación hematógena o linfática desde un foco primario de tuberculosis (la más frecuente), o c) la implantación directa a través del conducto auditivo externo [2,3]. Dado los antecedentes y ca-

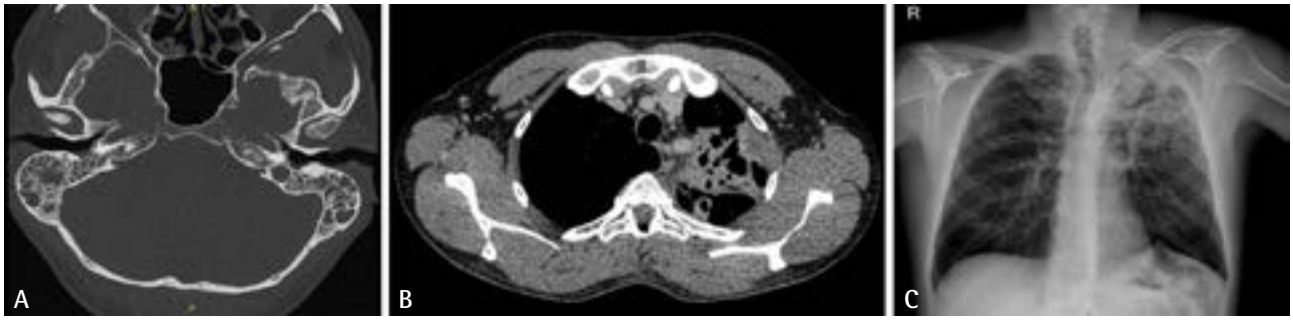

Figura 1 | **A. TAC craneal con ocupación bilateral de oído medio y celdillas mastoideas, B. TAC de tórax, LSI donde se aprecian algunas imágenes cavitadas y C. Radiografía de tórax con cavernas tuberculosas en LSI.**

racterísticas de nuestro paciente, la diseminación hematógena desde el foco pulmonar podría ser la causa de la otomastoiditis; sin embargo, la afectación bilateral de las otomastoides y el cultivo positivo de esputo nos hace sospechar que la aspiración a través de la trompa de Eustaquio sería una causa probable, facilitada por la inhalación de sustancias, aunque este hecho es más frecuente en niños por su anatomía [4].

La prueba de la tuberculina e interferón gamma pueden ayudar, pero el diagnostico se confirma por el cultivo y mediante el estudio de técnicas de amplificación de ácidos nucleicos. También es de gran utilidad el estudio histopatológico, que en nuestro caso no fue posible.

El diagnóstico de otomastoiditis media tuberculosa es tardío por tratarse de un proceso infeccioso raro y no muy frecuente. Sus manifestaciones clínicas son variables y faltan métodos diagnósticos sensibles y específicos. El retraso diagnóstico aumenta la morbilidad y las complicaciones pueden llegar a ser irreversibles; por lo que para evitar complicaciones graves es necesario iniciar tratamiento antibiótico rápidamente cuando exista alta sospecha clínica.

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Los autores no presentan ningún conflicto de intereses

BIBLIOGRAFÍA

1. Ramírez-Lapausa M, Menéndez-Saldaña A, Noguerado-Asensio A. Tuberculosis extrapulmonar, una revisión [Extrapulmonary tuberculosis]. Rev Esp Sanid Penit. 2015;17(1):3-11.. doi: 10.4321/S1575-06202015000100002.
2. Camino Ortiz de Barrón X, Toral Cegarra M, Goiburu Minguez S. Otitis media crónica supurativa por Mycobacterium tuberculosis. Un reto diagnóstico [Chronic suppurative otitis media by Mycobacterium tuberculosis. A diagnostic challenge]. Rev Esp Quimioter. 2018 Apr;31(2):182-183.
3. Muñoz A, Ruiz-Contreras J, Jimenez A, Maté I, Calvo M, Villafruela M, del-Pozo G. Bilateral tuberculous otomastoiditis in an immmunocompetent 5-year-old child: CT and MRI findings (2009: 3b). Eur Radiol. 2009 Jun;19(6):1560-3. doi: 10.1007/s00330-008-1130-7.
4. Nanda A, Zeki D, Parperis K. Chronic Suppurative Otitis Media Complicated With Mastoiditis: An Unusual Presentation of Tuberculosis. Am J Med Sci. 2016 Nov;352(5):544. doi: 10.1016/j.amjms.2016.02.026.