REVISTA ESPAÑOLA DE Quimioterapia

SPANISH JOURNAL
OF CHEMOTHERAPY
ISSN: 1988-9518
Volumen 37
Número 4
Agosto 2024
Páginas: 285-368

Publicación Oficial
de la Sociedad Española
de Quimioterapia

REVISTA ESPAÑOLA DE
Quimioterapia

Revista Española de Quimioterapia tiene un carácter multidisciplinar y está dirigida a todos aquellos profesionales involucrados en la epidemiología, diagnóstico, clínica y tratamiento de las enfermedades infecciosas

Fundada en 1988 por la Sociedad Española de Quimioterapia

Indexada en
Science Citation Index Expanded (SCI),
Index Medicus (MEDLINE),
Excerpta Medica/EMBASE,
Índice Médico Español (IME),
Índice Bibliográfico en Ciencias de la Salud (IBECS)

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28040 Madrid
revista@seq.es
Disponible en Internet:
www.seq.es

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www.seq.es

Publicación que cumple los requisitos de soporte válido

ISSN
0214-3429

e-ISSN
1988-9518

Depósito Legal
M-32320-2012

Maquetación
VicPG

Impresión
España

Esta publicación se imprime en papel no ácido.
This publication is printed in acid free paper.

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Quimioterapia

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/023.2024

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Meningococcal meningitis in Spain in the Horizon 2030: A position paper

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Article history
Received: 26 February 2024; Accepted: 15 March 2024; Published: 22 March 2024

ABSTRACT

Meningococcal meningitis (MM) and invasive meningococcal disease remain a major public health problem that generates enormous public alarm. It is caused by *Neisseria meningitidis*, a Gram-negative diplococcus with an enormous capacity for acute and rapidly progressive disease, both episodic and epidemic in nature, with early diagnosis and treatment playing a major role. It occurs at any age, but is most common in children under 5 years of age followed by adolescents. Although most cases occur in healthy people, the incidence is higher in certain risk groups. Despite advances in reducing the incidence, it is estimated that in 2017 there were around 5 million new cases of MM worldwide, causing approximately 290,000 deaths and a cumulative loss of about 20,000,000 years of healthy life. In Spain, in the 2021/22 season, 108 microbiologically confirmed cases of MM were reported, corresponding to an incidence rate of 0.23 cases per 100,000 inhabitants. This is a curable and, above all, vaccine-preventable disease, for which the World Health Organisation has drawn up a roadmap with the aim of reducing mortality and sequelae by 2030. For all these reasons, the Illustrious Official College of Physicians of Madrid (ICOMEM) and the Medical Associations of 8 other provinces of Spain, have prepared this opinion document on the situation of MM in Spain and the resources and preparation for the fight against it in our country. The COVID-19 and Emerging Pathogens Committee of ICOMEM has invited experts in the field to participate in the elaboration of this document.

Keywords: meningitis, meningococcus, meningococcal meningitis, *Neisseria meningitidis*, vaccines, prevention, epidemics, antimicrobial treatment, chemoprophylaxis.

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La meningitis meningocócica en España en el Horizonte 2030: Un documento de opinión

RESUMEN

La meningitis meningocócica (MM) y la enfermedad me-

ningocócica invasiva siguen siendo un importante problema de salud pública que genera una enorme alarma social. Está causada por *Neisseria meningitidis*, un diplococo Gram negativo con una enorme capacidad para producir una enfermedad aguda y de rápida evolución, tanto de carácter episódico como epidémico, en cuya evolución influyen enormemente el diagnóstico y el tratamiento precoces. Se presenta a cualquier edad, pero es más frecuente en niños menores de 5 años seguido de los adolescentes. Aunque el mayor número de casos se da en personas sanas, la incidencia es superior en determinados grupos de riesgo. A pesar de los avances en la reducción de la incidencia, se estima que en 2017 se produjeron alrededor de 5 millones de nuevos casos de MM en todo el mundo causando aproximadamente 290.000 muertes y una pérdida de unos 20.000.000 de años de vida sana acumulada. En España, en la temporada 2021/22, se notificaron 108 casos de MM con confirmación microbiológica, lo que corresponde a una tasa de incidencia de 0,23 casos por 100.000 habitantes. Se trata de una enfermedad curable y, sobre todo, prevenible con vacunas, para la que la Organización Mundial de la Salud ha elaborado una hoja de ruta con el objetivo de reducir su mortalidad y secuelas en 2030. Por todo ello, el Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) y los Colegios de Médicos de otras 8 provincias de España, han elaborado este documento de opinión sobre la situación del MM en España y los recursos y preparación para la lucha contra el mismo en nuestro país. El Comité de COVID-19 y Patógenos Emergentes del ICOMEM ha invitado a expertos en la materia a participar en la elaboración de este documento.

Palabras clave: Meningitis, meningococo, meningitis meningocócica, *Neisseria meningitidis*, vacunas, prevención, epidemias, tratamiento antimicrobiano, quimioprofilaxis.

INTRODUCTION

Meningococcal meningitis (MM) and invasive meningococcal disease (IMD) continue to be a major public health problem and cause for social alarm, since they can cause death within a few hours, especially in children and young people, who are generally previously healthy, with the appearance of fulminant clinical manifestations, and whose economic impact is high. The reasons for the social alarm it generates are various and can be summarized as follows: the disease has a worldwide distribution with epidemic potential, its lethality is still high, it entails high morbidity with complications during its course and a high percentage of survivors suffer sequelae [1-3].

Early diagnosis and management during the first hour of meningitis with meningococcal sepsis determine the success of treatment and control of its progression. The categorization of the patient and the assessment of his condition, monitoring and therapeutic opportunity, adapting the treatment to the severity of the condition, are fundamental.

Microbiological confirmation with the determination of the meningococcal serogroup is crucial for epidemiological surveillance, post-exposure prophylaxis of contacts and follow-up of possible vaccine failures. Blood and cerebrospinal fluid culture remains the reference method for microbiological diagnosis, but molecular tests are very useful in patients previously treated with antibiotics and results are rapid to obtain. The availability of the strain will make it possible to perform an antibiogram and to follow the evolution of *Neisseria meningitidis* resistance, as well as to carry out other sequencing studies of bacteriological and epidemiological interest [4].

Prevention by vaccination has been carried out since the 1970s with polysaccharide vaccines first, then with vaccines targeting the external membrane and, since 2000, with meningococcal conjugate vaccines. These are the conjugate vaccines against serogroups A, C, W, Y, the monovalent A and C (A marketed for Africa), and the tetravalent vaccine. In 2013, the first vaccine against serogroup B was licensed, which has completed the broad spectrum of global prevention of meningococcal disease by the five most frequent serogroups of the 12 existing ones.

Since 2023, infection by serogroup X, which in recent years has emerged in some countries in the "meningitis belt," is also immunopreventable by a pentavalent vaccine (ACWXY) that has been prequalified by the World Health Organization (WHO) for use in those countries. A second pentavalent vaccine (the first ABCWY), which is a combination of the tetravalent and meningococcal B vaccine, was licensed by the U.S. Food and Drug Administration (FDA) in October 2023 for use from 10 to 25 years of age.

Finally, it should be recalled that in November 2020, the 73rd Session of the WHO World Health Assembly approved the Defeating meningitis by 2030 roadmap for the world [5].

For all these reasons, the Illustrious Official College of Physicians of Madrid (ICOMEM) and 7 other medical colleges in Spain have decided to organize a day of discussion on the situation of meningococcal disease in the world and in Spain and the prospects for compliance with the WHO roadmap. The format consisted of two round tables in which a series of questions on this subject, previously formulated, were answered. The following document is the result of the deliberations of the day.

WHAT IS WHO'S POSITION ON ELIMINATING MENINGOCOCCAL MENINGITIS BY 2030? WHAT ROLE WOULD VACCINES PLAY?

Annually, more than 2.5 million people of all ages and from any country in the world suffer from bacterial meningitis, of which at least 10% may die. Among the survivors, 20% may have at least one or more long-term sequelae, with an enormous family, social, health and economic impact. Despite the strategies currently in place, health systems have not been able to reduce the number of cases in the same way as has occurred with other immunopreventable diseases such as tetanus or measles [5, 6].

WHO therefore developed a roadmap through a series of consultative meetings involving representatives from govern-

Table 1 **Comparative characteristics of meningococcal vaccines according to polysaccharide, conjugate and recombinant platforms based on outer membrane proteins. Adapted from Debbag et al. [10].**

Features	Polysaccharides	Conjugates	MenB recombinant
Effective in infants	✖	✔	✔
Induction of immune memory cells	✖	✔	✔
Hypo-response with booster dose	✔	✖	✖
Prevention in the acquisition of nasopharyngeal carriage of N. meningitidis	✖	✔	✖
Direct / Indirect Protection	✔ / ✖	✔ / ✔	✔ / ✖
Cross protection	✖	✖	✔

✖: absence of the described characteristic; ✔: presence of the described characteristic.
MenB recombinants: recombinant outer membrane protein vaccines against serogroup B

ments, public health agencies, academia, the private sector, and civil society. This roadmap was endorsed by the Strategic and Technical Advisory Group on Infectious Hazards and the Strategic Advisory Group of Experts on Immunization during 2019, and approved at the 73rd World Health Assembly in November 2020 [5, 7]. The work developed aims to establish a plan to address the main causes of acute bacterial meningitis (meningococcus, pneumococcus, *Haemophilus influenzae* and *Streptococcus agalactiae*), focusing on three visionary objectives that include eliminating epidemics of bacterial meningitis; to reduce the number of immunopreventable bacterial meningitis cases by 50% and deaths by 70%; and finally, to reduce disability and improve the quality of life of meningitis survivors, regardless of etiology. In order to achieve this, there are essential activities and milestones, which are summarized in five intertwined pillars: prevention and control of epidemics; disease surveillance; diagnosis and treatment; support and care for people affected by meningitis; and finally, advocacy and commitment to disseminate the importance of this issue globally, bringing together the different actors in a joint effort. [5].

The role that vaccines would play is described primarily in the epidemic prevention and control pillar, and includes increased and improved access to vaccines against meningococcus, pneumococcus and *H. influenzae* type b, increased vaccine coverage in target populations, development of new vaccines against these agents to increase their immunogenicity and spectrum of coverage, including a vaccine against *Streptococcus agalactiae*; improving prevention strategies and ensuring a timely and effective response to meningitis epidemics; all of which should be tailored to regional and local contexts [5].

Currently, several countries have implemented different vaccination strategies, considering the different direct and indirect protective properties of meningococcal vaccines (Table 1), which have proven to be successful in different parts of the world, according to data from their implementation in the real world [8]. At present, polysaccharide conjugate and recombinant vaccines are available in mono- and polyvalent formulations that can confer protection against serogroups A, B, C, W, X and Y . Recently, WHO promulgated its recommendation for the use of pentavalent vaccine against ACWXY serogroups in the meningitis belt in Africa, both at the programmatic and campaign levels, with updated recommendations for other countries worldwide expected by 2025 [9].

WHAT IS THE EXTENT OF MENINGOCOCCAL DISEASE IN THE WORLD?

Meningitis remains a major public health problem. It is endemic worldwide and causes occasional epidemics in different locations, with particular incidence in sub-Saharan Africa.

Although MM affects people of all ages, young children are most at risk, with half of all cases and deaths occurring in children under five years of age. In addition, one in five survivors of bacterial meningitis may have long-term sequelae: hearing loss, impaired vision, speech, language, memory and communication, seizures, paraparesis, scarring deformities and limb amputations. All of these result in a significant burden of disease, disability and reduced life expectancy in good health. Many cases could be prevented by vaccination.

Figures 1 and 2 [11], show the incidence and mortality, respectively, of meningitis per 100,000 inhabitants per year. As can be seen, the rates differ from one country to another.

Meningococcal meningitis epidemics are widespread in Africa in the so-called "meningitis belt" which stretches from Gambia and Senegal in the west to Ethiopia in the east and has a population at risk of approximately 450 million people in 26 countries. Epidemics are cyclical and usually coincide with the onset of the dry season and a strong dry wind called "harmattan: an ill wind that brings disease"[12]. It is the area of the world that bears the greatest burden of disease. In this African belt, serogroup A meningococcus accounted for more than 80% of cases during meningitis epidemics before the introduction of a meningococcal A conjugate vaccine in mass preventive campaigns (since 2010) and routine vaccination programs (since 2016). Three years later the incidence of this meningitis had decreased by 95% in vaccinated areas and has in fact been virtually eliminated in this area [13]. The first WHO prequalified pentavalent conjugate vaccine (MenFive) against

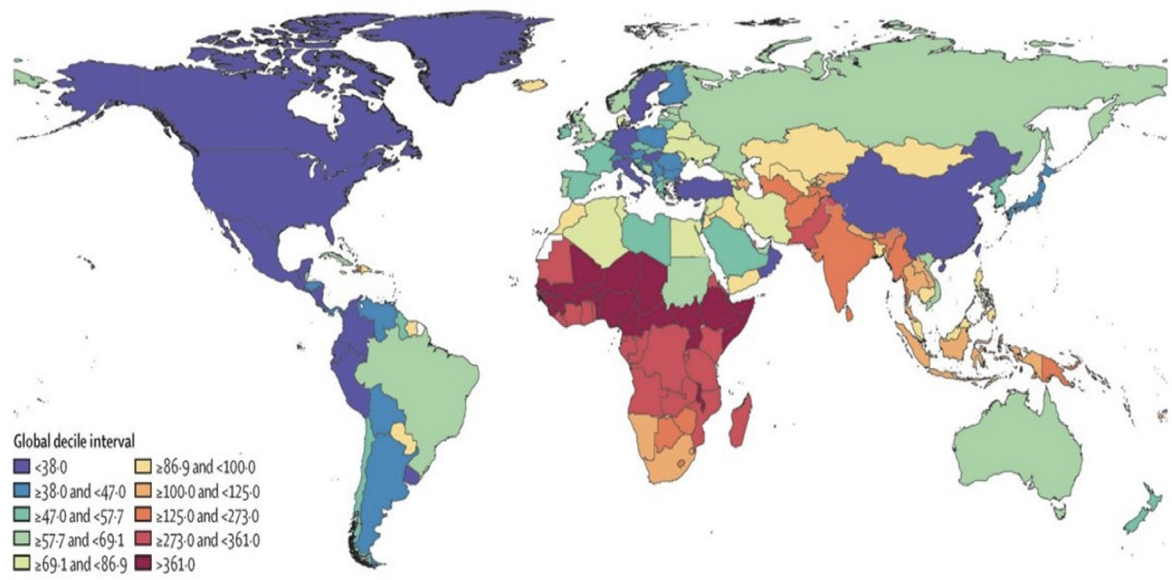

Figure 1 | **Incidence rate of meningitis per 100,000 population and year in children under 5 years of age (2019). Adapted from Global Burden of Disease Study 2019 [11]**

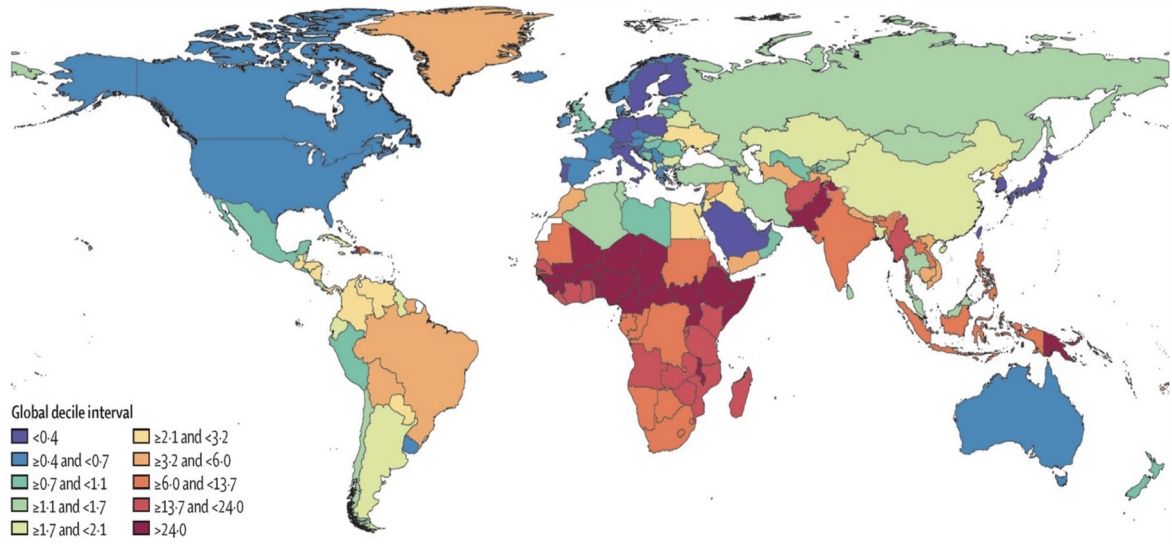

Figure 2 | **Meningitis mortality rate per 100,000 population and year in children under 5 years of age (2019). Adapted from Global Burden of Disease Study 2019 [11]**

the five predominant serogroups in Africa (A, C, W, Y and X) is currently planned for use [14].

As mentioned above, WHO launched the global roadmap "End Meningitis by 2030", which was adopted in 2020 [5] and has called for the establishment of a Global Meningitis Genome Partnership linking resources for: *N. meningitidis*, *S. pneumoniae*, *H. influenzae*, and *S. agalactiae* to improve global coordination in strain identification and tracking by optimizing resources.

Vaccination recommendations are established in two main groups: 1) for countries with high (>10 cases/100,000 inhab/year) or intermediate (2-10 cases/100. 000 inhab/year) and/or frequent epidemics of invasive meningococcal disease, the

recommendation is to establish large-scale meningococcal vaccination programs, and 2) for countries with low endemic rates (< 2 cases/100,000 inhab/year) the recommendation is meningococcal vaccination for defined risk groups.

WHAT ARE THE FIGURES FOR INVASIVE MENINGOCOCCAL DISEASE IN SPAIN AND ITS EVOLUTION IN RECENT YEARS?

Meningococcal disease has been notifiable in Spain since 1901. Currently, data are collected by the National Epidemiological Surveillance Network (RENAVE) managed by the National Epidemiology Center (CNE) integrated in the Carlos III Health Institute. The last RENAVE report that collects cumulative data on invasive meningococcal disease is from the 2021/22 season was published in the first quarter of 2023 in the Weekly Epidemiological Bulletin (BES) [15]. However, provisional data disaggregated by Autonomous Community (CCAA) are collected every week and published in the BES.

In Spain, 108 cases of meningococcal meningitis with microbiological confirmation were reported in the 2021/22 season. The incidence rate corresponds to 0.23 cases per 100,000 inhabitants with a slightly higher incidence in males (54.6%), with the youngest age group being the most affected (incidence rate of 5.16 in children under 1 year of age and 1.08 in the 1-4 year age group). Among the serogroups described, serogroup B was the most common, causing 48.1% (n=45, incidence 0.11) of the cases. This serogroup was followed by 6 cases of W, 5 of Y and 3 of C. Of note, 34.3% (n=37) of the cases were associated with nontypable or unknown serogroups. In the 2021/2022 season, the MM incidence rate dropped dramatically (0.14/100,000 population), with COVID-19 pandemic confinement being the most likely cause. The 2021/22 data are up to 72.6% lower than pre-pandemic (2018/19). In 2021/22 cases followed a typical seasonal pattern with the highest number of cases documented in the month of January.

By Autonomous Communities (AC) the highest number of cases per 100,000 inhabitants in 2021/22 occurred in the Basque Country (incidence 0.60), Cantabria (0.34), Castilla la Mancha (0.34), Andalusia (0.33) and Asturias (0.30) and the autonomous city of Ceuta (1.22) and there were ACs that did not report any cases (Aragon, Extremadura, La Rioja and the autonomous city of Melilla).

Preliminary data for 2022/23 indicate a clear upward trend, with 226 cases (incidence of 0.47)[16]. As in 2021/2022, the majority was serogroup B (105 cases, 46.5%, incidence 0.22) followed by W (25 cases, 11.1%, incidence 0.05), Y (18 cases, 8.0%, incidence 0.04) and C (3 cases, 1.3%, incidence 0.01).

WHAT ARE THE CHARACTERISTICS OF *N. MENINGITIDIS* IN SPAIN AND WHAT IS ITS RELATIONSHIP WITH THE EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE?

The epidemiology of MM, both in Spain and globally, has always been unpredictable due to the changing nature of the causal microorganism, *N. meningitidis*, which causes epidemic waves and inter-epidemic periods generally associated with the circulation of certain hypervirulent strains [17]. This classical image of IMD has been greatly altered by the use of vaccines that in some cases provide not only individual protection but also herd immunity with enormous public health impact. This ability to produce herd immunity is only associated with polysaccharide conjugate vaccines (A, C, Y and W) but is not achieved with the use of protein formulation vaccines (B). In this context, and until 2019, the situation in Spain was one of a slow but sustained increase of serogroups W and Y, which in that year together reached 45% of the total number of confirmed cases received in the Reference Laboratory, with cases of serogroup B (historically the majority in Spain), 44.2%, with an overall rate of IMD collected by the RENAVE of 0.83 cases per 100,000 inhabitants, which confirmed a growing trend observed in the previous 4 years. It should be noted that the high percentage of non-typeable isolates or isolates with unknown serogroups mentioned in the previous question are probably an artifice, since the data were not included at the time of reporting, so that the distribution by serogroups is probably better reflected by taking the data from the ISCIII meningococcal reference laboratory as a source.

With the arrival of the COVID-19 pandemic in 2020, and associated with the containment measures to reduce the transmission of the SARS-COV-2 virus, in Spain, as in other countries around the world, there was a marked decrease in the incidence not only of IMD but also of *S. pneumoniae or H. influenzae* as reflected in the data of the International Consortium "Invasive Respiratory Infection Surveillance (IRIS)" in which the Reference Laboratory of Spain actively collaborates. This decrease can be observed especially in the year 2021, with an incidence rate of only 0.14 X 10^5 in the year 2021, with such a small number of cases that it is impossible to draw conclusions with statistical significance. As the containment measures related to the pandemic have been relaxed, the number of cases has been slowly increasing so that in 2023, the number of cases is slightly higher than that observed in 2020, and the distribution of serogroups again shows similar values. There are other factors that could have had an impact on the overall decrease in cases of IMD, which are probably more difficult to evaluate, such as the use in private pediatrics of a serogroup B vaccine with a protein formulation in children outside the vaccination schedule (not funded) until 2022, the introduction of this vaccine in the schedule (funded) from 2023, without forgetting a saturation of the surveillance services due to the pandemic that could be responsible for a limited and difficult to quantify loss of registered cases.

No significant differences were observed in the circulating clonal complexes before and after the pandemic, nor in the distribution of antigens included in the available vaccines against serogroup B in the strains isolated from invasive processes.

Table 2 **Microbiological techniques used in the diagnosis of meningococcal meningitis and invasive meningococcal disease.**

Techniques	Comments
Conventional diagnosis	
Gram stain	Rapid result, operator-dependent sensitivity and bacterial load.
Latex agglutination	In disuse due to its low sensitivity.
Culture	Variable sensitivity depending on bacterial load. Necessary for further sensitivity and typing studies (serogroup).
Susceptibility study	Difficulties in culture medium.
Isolates typing	Seroagglutination against polysaccharide capsule antigens. Indispensable for vaccine design and monitoring of possible vaccine escapes
Molecular diagnostics	
Syndromic panels	Versatile (detection of various pathogens), low handling. Rapidity.
Whole genome sequencing (WGS)	Analysis of protein variable regios (PorA, PorB, FetA), coreMLST (cMLST), core gene SNVs (cgSNVs) Knowledge of the resistome

WHAT IS THE ROLE OF NEW TOOLS IN THE DIAGNOSIS OF INVASIVE MENINGOCOCCAL DISEASE? ARE THEY INFLUENCING REGISTRATION?

The microbiological diagnosis of IMD has changed radically in recent years with the introduction of the so-called molecular techniques based on the amplification of nucleic acids, thus gaining greater sensitivity [18] (Table 2). Previously, this diagnosis was based exclusively on direct sample staining, essentially Gram staining, and microbiological culture of cerebrospinal fluid, blood cultures or some tissues with a highly variable sensitivity depending on the microorganism and bacterial load (10-95%). Rapid immunological techniques based on agglutination with latex particles or immunochromatography were also used, also with a very variable sensitivity [19].

Currently, the most effective methods in the diagnosis of IMD are the so-called syndromic panels that amplify several targets covering different pathogens, including bacteria, fungi and viruses and even resistance markers. They also have the advantage over culture in obtaining results in a short time (less than 90 minutes). The most widespread are based on real-time PCR (RT-PCR) or isothermal amplification (LAMP). Despite their sensitivity and high negative predictive value, they are not free of false-positive results, although they do not usually occur with N. meningitidis [19, 20].

The introduction of these molecular techniques has improved microbiological diagnosis, transforming probable and suspected cases into confirmed cases (with microbiological diagnosis). However, microbiological culture continues to be the reference in the diagnosis of IMD as it allows strain recovery and subsequent sensitivity study.

Serogroup typing is traditionally performed by slide agglutination test with sera containing antibodies against the different capsular antigens. In Spain, serogroup typing is performed by the microbiology laboratory itself or by the National Reference Laboratory for Meningococci of the Instituto de Salud Carlos III.

The notification of the microbiological results to the Public Health authorities takes place almost in real time through the computer systems of the laboratories and Microbiology Services. Given the importance of IMD, this speed in the transmission of results must be preceded by the availability of microbiology laboratories with continuous attention (also called 24/7) that ensure microbiological diagnosis with both culture and molecular techniques [21].

Currently, other typing techniques are also being added to serogroup knowledge, including the amplification of specific sequences of variable regions (PorA, PorB, FetA) in conjunction with MLST (multilocus sequence typing) schemes [22]. The introduction of whole genome sequencing (WGS) techniques, including from direct samples, will provide a better understanding of the epidemiology of *N. meningitidis* and its spread [23]. A recent study analyzed nearly 70,000 sequences of *N. meningitidis* deposited in open access databases, demonstrating the usefulness of these studies in the knowledge of the global epidemiology of this pathogen, the identification of epidemic clones and their temporal dispersion, as well as possible evolutionary trajectories [24].

IS IT POSSIBLE TO SUMMARIZE THE FACTORS THAT INCREASE THE RISK OF MENINGOCOCCAL MENINGITIS?

The highest incidence occurs in children under 5 years of age (especially under one year of age), with a second peak among adolescents and young adults, who are also the main carriers and transmitters of the disease. Meningococcus has a

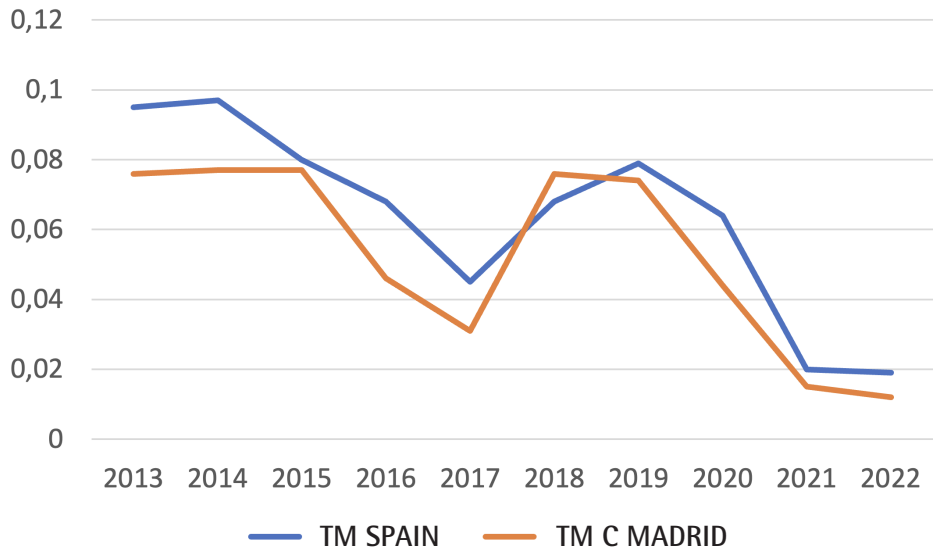

Figure 3 Rate of deaths per 100,000 inhabitants caused by Invasive Meningococcal Disease in Spain and the Community of Madrid. Prepared by the General Directorate of Public Health of the Community of Madrid

TM, Total Mortality and TMC , Total Mortality Community of Madrid

special predilection for the extreme ages of life, with people over 64 years of age being the next most important age group.

Predisposing diseases include: anatomical or functional asplenia, complement factor deficiency, treatment with eculizumab or ravulizumab, hematopoietic stem cell transplant recipients, patients with HIV infection, patients with previous episodes of IMD by any serogroup, and contacts of an index case of IMD by serogroup A, B, C, W or Y [25].

Another risk factor is travel to countries with a high incidence, especially sub-Saharan African countries or the pilgrimage to Mecca.

WHAT IS THE MORTALITY RATE OF MENINGOCOCCAL MENINGITIS AND ITS SEQUELAE IN OUR ENVIRONMENT?

Analyzing the period 2019-2023, the incidence of IMD in the Community of Madrid (CM) has presented a notable decrease, similar to the rest of Spain, partially explained by the application of SARS-CoV-2 containment measures (from March 2020), which resulted in a decrease in the incidence of respiratory-transmitted infectious diseases, in addition to, by the inclusion in the vaccination schedule of the Men ACWY vaccine in adolescents.

The mortality rate (number of deaths per hundred thousand inhabitants) for this heading is low, both in the Community of Madrid and in Spain as a whole (Figure 3).

In this disease, given its severity, it is important to analyze the lethality data (deaths due to meningococcal disease/EMI cases), which in the last five-year period (2019-2023) ranges between 8-15% in the Community of Madrid. The overall case fatality rate can be seen in Table 3.

Table 3 Meningococcal disease fatality rate in Spain. Seasons 2012-13 to 2022-23.

Year	Spain (%)
2012-13	10.5
2013-14	10.2
2014-15	10.6
2015-16	10.1
2016-17	10.7
2017-18	12.1
2018-19	10.1
2019-20	12.0
2020-21	6.1
2021-22	7.0
2022-23*	6.0

Prepared by the authors based on the weekly epidemiological bulletin ISCIII [15]
*Provisional data.

Of the total number of reported cases of MM in the 2022-2023 season, 6 deaths were reported, 3 caused by serogroup B, 1 by other serogroups, 1 by unknown serogroup and 1 non-typeable.

During the 2109-20 and 2020-2021 seasons, the age group with the highest case-fatality rate was the over 84 years old (26.7% and 28.57%, respectively) and the group with the lowest case-fatality was the 1-4 years old (5.56%). During the 2021-22 season, the age group with the highest case fatality rate was 45-64 years (20%). In the age groups under 1 year, 1-4 years, and 10-14 years, the case fatality rate was 0%.

In the five-year period 2019-2023 in the Community of Madrid, the evolution of most of the cases has been favorable, although 10% of the cases presented sequelae in the five years of follow-up of the study. The sequelae in these cases were as follows: 43% (6 cases) of the cases had hypoacusia, 4 cases in patients over 65 years of age; 28% (4 cases) had partial amputations of lower limbs (2 cases), total amputation of a foot (1 case), amputation of distal fingers (1 case), hydrocephalus (1 case), renal failure (2 cases) and subacute myopathy (1 case).

COULD AGE BE A DETERMINANT IN PRODUCING A DELAY IN DIAGNOSIS?

During the five-year period 2019-2023 there has been no significant delay in diagnosis in any age group. All cases reported to the Community of Madrid have required admission to a hospital. To assess the delay, the difference between the reported date of symptom onset and the date of hospital admission was analyzed. The mean was 1.6 days and the median 1 day.

However, atypical presentation of IMD in adults older than 55 years is described, often linked to a comorbid condition, including myocarditis/endocarditis and arthritis. Initially in these cases, IMD was not suspected and *N. meningitidis* was detected once the patients were admitted to the hospital [26].

Atypical presentation of IMD may result in diagnostic delay. The comprehensive review by Guedes et al. [26], found evidence that IMD in older adults is caused mainly by serogroups that are not generally predominant circulating strains (W and Y), and have a higher case fatality rate as well as a higher likelihood of atypical symptoms.

WHAT ARE THE MOST IMPORTANT FEATURES OF ANTIMICROBIAL TREATMENT OF MENINGOCOCCAL MENINGITIS? IS ANTIMICROBIAL RESISTANCE A PROBLEM?

It is well known that delay in diagnosis and initiation of antibiotic treatment is directly related to increased mortality in MM [27]**.** Therefore, its administration should not be delayed and should be started as soon as possible after the extraction of samples for microbiology, even before performing a cranial CT scan and lumbar puncture if these will delay the start of the antibiotic.

In this regard, it should be borne in mind that only 40% of MM cases present with the classic triad of fever, headache and neck stiffness, which can make it difficult to diagnose patients and delay the initiation of antibiotic treatment [27]. A review of the literature showed that the association between delay in antimicrobial administration and patient prognosis depended primarily on the clinical presentation, such that this relationship was lost when the patient did not present altered consciousness or the classic clinical triad [28]. The accentuation of headache with exploratory maneuvers is considered positive if the headache is exacerbated by turning the head horizontally two or three times per second. The maneuver is intended to rule out meningitis without the need for lumbar puncture [29].

The choice of antibiotic treatment for invasive infection by *N. meningitidis* is based, as for any serious disease, on the choice of a potent antimicrobial, with high bactericidal capacity, with a low rate of resistance in the community for this microorganism, pending the antibiogram, and on its ability to spread to the infectious focus.

In relation to sensitivity, resistance to antibiotics used in the treatment and prophylaxis of meningococcal disease is relatively rare in Spain. The antibiotic with the highest percentage of resistance is penicillin, around 10%. Resistance to third generation cephalosporins is rarely reported. However, in about 1% of cases, strains with reduced sensitivity to both cefotaxime and ceftriaxone have been observed [30, 31]. Finally, it should be noted that resistance to rifampicin has been reported among meningococci, mainly after prophylaxis, and resistance to ciprofloxacin, although this is rare [32].

In relation to diffusion to the focus, in the case of meningitis it is necessary to take into account the difficulty of some antibiotics to cross the blood-brain barrier (BBB) and reach sufficient concentrations in the cerebrospinal fluid (CSF). The penetration of the antibiotic will depend on its molecular size (the lower the molecular mass, the greater the ease of diffusion), liposolubility (which favors diffusion), binding to plasma proteins (the lower the binding, the more free drug to reach the CSF) and its affinity for BBB transporter proteins, which expel the antibiotic as efflux pumps. However, MM is an inflammatory disease that favors antibiotic penetration through BBB due to effacement of the intercellular sealing of the endothelium, moderate reduction of CSF production and reabsorption, and decreased activity of transporter proteins, which are inhibited by the presence of inflammatory cytokines [33].

Beta-lactams are molecules of low molecular mass, with variable binding to plasma proteins, low liposolubility and variable affinity for efflux pumps. In the absence of meningeal inflammation their penetration is relatively low, 10-20%, but the concentration they reach in CSF in a situation of meningeal inflammation is sufficient to exceed the MIC of sensitive pathogens. In addition, ß-lactams have a relatively low toxicity, so that the dose administered can be increased to ensure high concentrations in CSF without assuming a high risk of adverse effects [33]. Based on the above, the antibiotic treatment of choice for meningococcal meningitis is the administration of third-generation cephalosporins (ceftriaxone 2g/12h or cefotaxime 2-4 g/4-6h intravenous in adult). The alternative in patients allergic to cephalosporins would be aztreonam 2g/6h intravenous. Quinolones are small molecules, moderately li-

Table 4 Chemoprophylaxis of contacts of patients with meningococcal meningitis.

Rifampin[a]	Adult: 600 mg every 12 h orally, for 2 days Children 1 month to 12 years: 10 mg/kg/12 h orally, for 2 days Children < 1 month: 5 mg/kg/12 h orally, for 2 days
Ciprofloxacin[b]	Adult: 1 dose of 500 mg orally
Ceftriaxone[c]	Adult: 1 dose of 250 mg intramuscularly Children < 12 years: 1 dose of 125 mg intramuscularly

[a]Not recommended in pregnancy and lactation. Contraindicated in severe hepatic insufficiency. Decreases the efficacy of oral contraceptives.
[b]Ciprofloxacin is contraindicated in pregnant, lactating and < 18 years old.
[c]Useful in pregnancy and lactation.

posoluble and with low binding to plasma proteins. Concentrations in CSF can reach 40% for ciprofloxacin and 80% for levofloxacin and moxifloxacin [33]. *N. meningitidis* is very sensitive to ciprofloxacin and levofloxacin and these drugs are an alternative in patients allergic to beta-lactams.

MM may be accompanied by sepsis requiring specific management [34, 35]. In these cases, patients must be monitored, ensure adequate oxygenation, sometimes requiring intubation, administer fluid therapy or vasoactive drugs to maintain adequate tissue perfusion and treat any complications that may arise, such as hypoglycemia, ionic alterations, coma or intracranial hypertension.

Finally, it should be noted that the administration of dexamethasone decreases the rate of complications, and even mortality, in patients with meningitis due to *H. influenzae,* pneumococcus or tuberculosis when it is administered before the first dose of antibiotic or no later than one hour after its administration. However, it has not shown any benefit in MM [31].

WHAT SHOULD BE THE ANTIMICROBIAL PROPHYLAXIS OF THE COHABITANTS AND ASSISTANTS OF PATIENTS WITH MENINGOCOCCAL MENINGITIS?

The aim of meningococcal chemoprophylaxis is to eliminate the possible nasopharyngeal carrier status of the contact and break the chain of transmission, as well as to protect the individual from developing the disease. It is estimated to reduce the risk of transmitted meningococcal disease by 90% [36].

It should be performed in children and adults who have lived with the index case during the 7 days prior to the onset of symptoms and up to 24 hours after initiation of appropriate antibiotic treatment. It should be administered as soon as possible and as long as 10 days or more have not elapsed since contact.

Only cohabitants or close contacts should receive chemoprophylaxis, considering these to be those who have had prolonged contact (more than 8 hours) with the patient, close (less than 3 meters) or who have been directly exposed to the patient's oral secretions [31,36,37]. In the case of healthcare personnel, brief, non-intimate transient contacts are excluded, unless they have participated in cardiopulmonary resuscitation maneuvers, endotracheal intubation or aspiration of respiratory secretions.

Chemoprophylaxis is summarized in Table 4. The antibiotic of choice is rifampicin in all age groups, which reduces the carrier rate by up to 96%. An alternative in adults is ciprofloxacin, but it is not recommended during pregnancy, lactation or in growing children and adolescents. The advantage over rifampicin is that it is administered in a single oral dose. For this reason, it can be used as a first choice in groups of adults where difficulties in administration or follow-up are foreseeable. Finally, ceftriaxone is another alternative, especially in case of pregnancy and lactation, if it has been decided to administer chemoprophylaxis.

WHAT VACCINES ARE AVAILABLE AGAINST INVASIVE MENINGOCOCCAL DISEASE? WHO SHOULD RECEIVE THEM? WITH WHAT GUIDELINES?

Eight meningococcal vaccines are currently available in Spain. Six of them are polysaccharide conjugates and the other two against serogroup B are prepared from subcapsular proteins [38-40] (Table 5). In the conjugates, the oligo- or capsular polysaccharide of the different serogroups binds to a carrier protein that can be tetanus toxoid or a mutant of diphtheria toxoid (CRM197). Among them, there are three that are monovalent against serogroup C (MenC): Menjugate, Meningitec and NeisVac-C and three tetravalent against serogroups A, C, W and Y (MenACWY): MenQuadfi, Menveo and Nimenrix. The "C" component of these tetravalent vaccines generates immunity similar to that of monovalent vaccines against that serogroup and can replace them in the vaccination regimens in which they are used. Both Meningitec and Menjugate are currently out of use in our country, in favor of NeisVac-C, the only vaccine against MenC that allows the administration of a single dose during the first year of life. There are two vaccines authorized against meningococcal B, one from 2 months of age (Bexsero) and the other from 10 years of age (Trumenba) (Table 5).

Table 5 **Authorized vaccines in Spain against meningococcus.**

Brand name	Serogrups	Active principle	Transporter protein	Adyuvant	Minimum age of use
Menjugate (GSK)	C	10 µg capsular oligosacáride, group C	12,5-25 µg CRM197	0,3 a 0,4 mg aluminum hydroxide	2 months
Meningitec (Nuron Biotech)	C	10 µg capsular oligosaccharide, group C	15 µg CRM197	0,125 mg de aluminum phosphate	2 months
NeisVac-C (Pfizer)	C	10 µg capsular polysaccharide (de-O-acetylated) of group-C	10-20 µg tetanus toxoid	0,5 mg de hydrated aluminum hydroxide	2 months
MenQuadfi (Sanofi Pasteur)	A, C, W, Y	10 µg capsular polysaccharide of groups A, C, W and Y	55 µg tetanus toxoid	-	12 months
Menveo (GSK)	A, C, W, Y	10 µg capsular oligosaccharide of group A and 5 µg oligosaccharide of group C, W and Y	16,7-33 µg CRM197 (A) 7,1-12,5 µg CRM197 (C) 3,3-8,3 µg CRM197 (W) 5,6-10 µg CRM197 (Y)	-	2 years
Nimenrix (Pfizer)	A, C, W, Y	5 µg capsular polysaccharide of groups A, C, W and Y	44 µg tetanus toxoid	-	6 weeks
Bexsero (GSK)	B	50 µg recombinant fusion protein NHBA\50 µg recombinant protein NadA\50 µg recombinant fusion protein fHbp\25 µg OMV Neisseria meningitidis B (PorA P1.4)	-	0,5 mg aluminum hydroxide	2 months
Trumenba (Pfizer)	B	60 µg fHbp lipidated subfamily A (A05) of Neisseria meningitidis B\60 µg fHbp lipidated subfamily B (B01) of Neisseria meningitidis B	-	0,25 mg aluminum phosphate	10 years

The posology, indications and ages of use of these vaccines may undergo imminent changes depending on studies currently underway and reviews of the EPAR by the European Medicines Agency. The first pentavalent meningococcal vaccine, ABCWY (Pfizer), has recently been approved by the American FDA but is not yet available in our country. This vaccine is authorized only for persons aged 10 to 25 years.

The Spanish Interterritorial Council includes in its current meningococcal vaccination recommendation systematic vaccination against meningococcal C in infants at 4 and 12 months, against meningococcal ACWY at 12 years of age, and against meningococcal B in infants at 2, 4 and 12 months of age. Outside these ages, vaccination would only be indicated in specific risk groups, which we listed above, specifically B and ACWY in asplenia, complement deficiencies and treatment with eculizumab, hematopoietic progenitor transplantation, personal history of invasive meningococcal disease and laboratory personnel exposed to meningococcus, and ACWY in HIV.

WHAT WOULD BE THE IDEAL VACCINATION SCHEDULE?

It is not easy to establish the ideal meningococcal vaccination schedule, and only in Europe is there a wide variety, and the differences cannot be explained by epidemiological or logical criteria. In the opinion of some of the authors of this manuscript, the best is the most complete, and should cover both serogroup B and ACWY, and include at least both infants and adolescents (Figure 4). Vaccination of adolescents against ACWY is known to work in the medium term, based on the class effects of conjugate vaccines on carriers, and also the positive objective results of this strategy in the UK. However, with current coverages, it is not possible to count on indirect protection of unvaccinated subjects, except for serogroup C. Once indirect protection is achieved in the community through high and maintained coverage in the ACWY adolescent cohort, infant doses could be omitted. In the case of meningococcus B, since there is no impact on carriers, protection would always be direct. There are no objective data to confirm that a booster dose of meningococcus B is necessary in older children or adolescents correctly vaccinated as infants, nor that a single dose at this age is sufficient to maintain protection or to obtain the potential benefits of cross-protection described in the literature for this age group. Nevertheless, vaccination of adolescents against meningococcal B is important because of their protection as the second group with the highest incidence of meningococcal disease, and it is also possible that through the cross-protection that these protein vaccines can generate, a certain degree of clinical protection against gonorrhea, a disease that is on the rise and for which there are no specific vaccines.

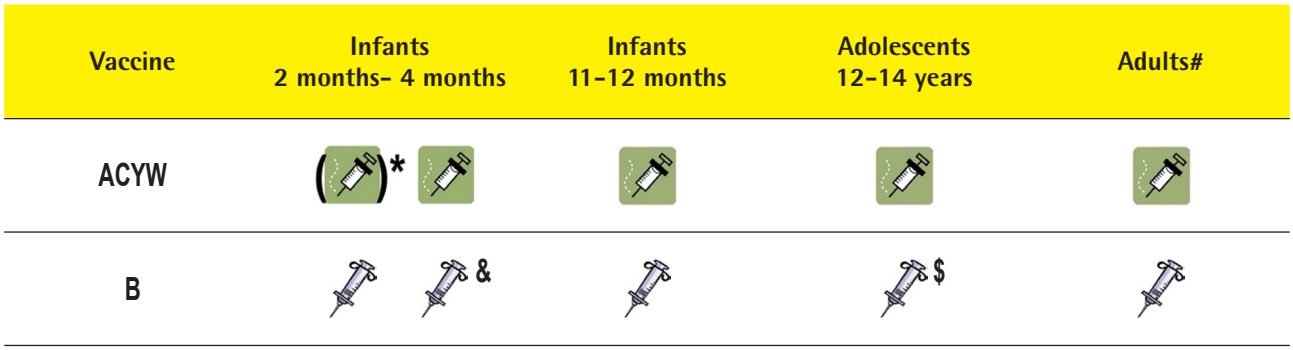

Figure 4 | **Most complete meningococcal vaccination schedule according to the vaccines currently available. The application of this schedule is subject to the technical data sheets of the vaccines according to the age at which they are administered, as well as to the epidemiological context. Adapted from Martinón-Torres et al. [41,42]**

* According to current data sheets, vaccination of infants under 6 months of age requires at least two doses of primary vaccination. Replacing the current 4-month monovalent C dose with ACWY would be sufficient for protection against serogroup C. The results of a clinical trial evaluating the 1+1 schedule with ACWY-TT (Nimenrix) at 3 and 12 months of age have recently been reported, showing its safety and immunogenicity. It could be considered to progressively dispense with the infant doses against ACWY, once indirect protection in the community has been achieved through high and maintained coverage in the cohort of adolescents with ACWY, as was done in the past with the monovalent vaccine doses against C in infants.

& The second dose of meningococcal B could be administered as early as 3 months of age in the 3-dose primary vaccination schedule. In the 2-dose regimens, the minimum interval between doses is 8 weeks according to the technical data sheet.

$ This dose could be administered at 12 or 14 years of age, taking advantage of other vaccination visits. We do not yet have data to justify the need for a booster dose of meningococcal B in children who have been correctly primed, nor that a dose at this age is sufficient to maintain adequate levels of protection or to obtain the potential benefits of cross-protection described in the literature for this age group.

Information on meningococcal vaccination in adults is limited and restricted to its use in specific risk groups. We do not know the persistence of the protection of childhood primovaccination in adults. More data are needed to justify routine adult vaccination as part of a vaccination schedule.

Older adults face the highest mortality rates associated with invasive meningococcal disease, which could be attributed to multiple factors, including the presence of comorbidities and the manifestation of atypical clinical symptoms that complicate early diagnosis and treatment. Although incidence rates are lower than in childhood, the increase in invasive meningococcal disease in older adults is objective and particularly worrisome due to the progressive increase in the elderly population worldwide, so more research is needed to determine the most effective and efficient vaccination strategies and to provide a solid basis for health authorities to decide on the expansion of national immunization programs to protect this age group. In any case, although there is limited information on the long-term protection of the available meningococcal vaccines, it is important to note that the following information is not yet available [26, 41]. Adult meningococcal vaccination should be considered as part of a meningococcal disease eradication program [42-44].

MM is only one, but it is caused by different serogroups, and today there are safe and effective vaccines that cover practically all the cases that occur in our country. In the opinion of some of the authors of this work, if we really want to control meningococcal disease and work decisively towards a world free of meningitis by 2030, the official calendar should move in the direction of this broader proposal, providing coverage against all possible serogroups and protecting both infants and adolescents. At the present time, the meningococcal vaccination schedule closest to the "ideal" in Spain, in the opinion of some of the authors of this study, is that of the autonomous community of Galicia, which includes vaccination against ACWY at 4 months, 12 months and 12 years, against B at 2, 4 and 12 months, and should only include vaccination against meningococcal B in adolescents to complete it (not a unanimous opinion) [2] (Figure 4).

CAN PROTECTION AGAINST OTHER PATHOGENS BE EXPECTED FROM VACCINATION AGAINST MENINGOCOCCUS?

As mentioned above, the polysaccharide A, C, Y and W conjugate vaccines provide not only individual protection, but also indirect protection [45] which has an enormous impact on public health. Herd immunity is not achieved with the use of protein-formulation vaccines, such as those directed against meningococcal B [46]. However, the subcapsular antigens contained in the 4CMenB vaccine are present to a greater or lesser extent in other serogroups of Neisseria meningitidis, so it is possible that the vaccine could offer some degree of protection against IMD due to serogroups other than B [47].

On the other hand, the 4CMenB vaccine could offer a certain degree of cross-protection against gonococcus based on the fact that *N. meningitidis* and *N. gonorrhoeae* are very

similar in genetic and antigenic terms, with 80-90 % nucleotide identity in the genome. Of the 22 major proteins of the outer membrane vesicles (OMVs) of meningococcus, 20 have homologues in gonococcus. In addition, the meningococcal NHBA antigen has a surface-exposed and highly conserved homologue in gonocococcal strains, with 67 % identity. Several studies [48-50] have shown some protection against gonorrhea from meningococcal vaccines with OMV in their composition. The results of these studies support ongoing randomized controlled trials [51, 52] on the efficacy of 4CMenB against gonorrhea.

WHAT IS THE ROLE OF PATIENT ASSOCIATIONS IN SPAIN?

The Spanish Association Against Meningitis (AEM) is the only one in Spain that fights against Meningitis as its main mission. The role of the AEM is aligned with the WHO's global plan to work to reduce the disease by 2030. In fact, as members of CoMO (Confederation of Meningitis Organizations) the AEM was invited in 2018 to draft in London, the main pillars to achieve that end.

The scientific committee of the AEM is coordinated by Dr. Federico Martin Torres, and its messages reach the general population with truthful and science-based information on the signs and symptoms of this disease and on the benefits of vaccination to prevent it.

There is also a network of volunteers that includes affected families who lead the representation of the AEM in their region or community, as well as a team of mental health professionals such as psychiatrists, psychologists, therapists, and occupational therapists who offer free support to affected families, both individually and collectively.

It is important to highlight the diversity of funding received by the AEM, since thanks to the solidarity events and the support of companies from different sectors, both public and private, can reach families in need with grants that for example in 2023 reached 20,000 €.

The AEM is, therefore, a non-profit organization whose mission is to support research and families affected by this disease. It will soon be eight years old with a large presence in media and social networks reaching thousands of people. Being the only patient association that spreads the benefits of prevention through vaccines places the AEM in a very high first level, which does not prevent us from being aware of the responsibility of this situation.

The AEM also fulfills a fundamental and very new role in patient associations: "Advocacy" or institutional relations. Until now, the ability to reach politicians and health authorities was limited, but thanks to a great deal of training and help from its English counterparts, the AEM has managed to understand the language, the moment, and the way to present petitions to politicians. Proof of this is the photo of the steps of the Parliament of Catalonia in November 2022, where they managed to make the Minister understand the seriousness of the consequences of this disease and decided a few months later to vaccinate infants born in Catalonia against one of the most common serogroups of meningococcus.

FUNDING

None to declare

CONFLICTS OF INTEREST

The author declares no conflicts of interest

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Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
doi:10.37201/req/037.2024

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Clinically important pharmacokinetic drug-drug interactions with antibacterial agents

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Article history
Received: 13 April 2024; Revision Requested: 1 May 2024; Revision Received: 6 May 2024;
Accepted: 14 May 2024; Published: 5 June 2024

ABSTRACT

Antimicrobial agents are widely used, and drug interactions are challenging due to increased risk of adverse effects or reduced efficacy. Among the interactions, the most important are those affecting metabolism, although those involving drug transporters are becoming increasingly known. To make clinical decisions, it is key to know the intensity of the interaction, as well as its duration and time-dependent recovery after discontinuation of the causative agents. It is not only important to be aware of all patient treatments, but also of supplements and natural medications that may also interact. Although they can have serious consequences, most interactions can be adequately managed with a good understanding of them. Especially in patients with polipharmacy it is compulsory to check them with an electronic clinical decision support database. This article aims to conduct a narrative review focusing on the major clinically significant pharmacokinetic drug-drug interactions that can be seen in patients receiving treatment for bacterial infections.

Keywords: Anti-Bacterial Agents, Drug Interactions, Pharmacokinetics, Beta-Lactams, Sulfonamides, Macrolides, Quinolones, Glycopeptides, Rifamycins.

Interacciones farmacocinéticas clínicamente relevantes con agentes antibacterianos

RESUMEN

Los antimicrobianos se utilizan ampliamente y las interacciones farmacológicas representan un desafío debido al aumento del riesgo de efectos adversos o la reducción de la eficacia. Entre las interacciones, las más importantes son aquellas que afectan el metabolismo, aunque aquellas que involucran a los transportadores de fármacos están siendo cada vez más reconocidas. Para tomar decisiones clínicas, es fundamental conocer la intensidad de la interacción, así como su duración y la recuperación dependiente del tiempo después de la discontinuación de los agentes causantes. No solo es importante estar al tanto de todos los tratamientos del paciente, sino también de los suplementos y medicamentos naturales que podrían interactuar. Aunque pueden tener consecuencias graves, la mayoría de las interacciones pueden manejarse adecuadamente con un buen entendimiento de las mismas. Especialmente en pacientes con polifarmacia, es obligatorio verificarlas con una base de datos electrónica de apoyo a la decisión clínica. Este artículo tiene como objetivo realizar una revisión narrativa centrada en las principales interacciones farmacocinéticas farmacofarmacéuticas de importancia clínica que pueden observarse en pacientes que reciben tratamiento para infecciones bacterianas.

Palabras clave: Agentes antibacterianos, interacciones farmacológicas, farmacocinética, betalactámicos, sulfonamidas, macrólidos, quinolonas, glucopéptidos, rifamicinas.

INTRODUCTION

When a patient is hospitalized for an urgent illness, it should be taken into consideration that could probably require medication for other comorbidities, including infections. The possible interaction between these drugs is an important aspect when planning treatment. In patients with polypharmacy, the risk of interactions increases with the addition of new drugs. Studies indicate that between 37-60% of patients may present an interaction during hospital admission, which may cause a loss of efficacy or increased adverse effects [1]. A Turkish multicenter study reported the frequency and potential drug-drug interactions (DDI) in five hospitals. More than 25% of all interactions were associated with antimicrobial agents

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[1]. Not only DDIs are relevant, but also food, vitamins/mineral supplements, and natural products could interact with drugs, increasing adverse effects or otherwise reducing efficacy [2,3].

DDIs usually involve an object drug (victim) and a precipitant drug (perpetrator) that modifies the effect of the object drug. Occasionally a pair of drugs will interact in both directions through one of these two general mechanisms [4].

Pharmacokinetic (PK) interactions occur when the precipitant drug changes the object drug's absorption, distribution, metabolism, or excretion. These interactions are typically managed by monitoring drug concentrations or vital signs [5,6].

Pharmacodynamic (PD) interactions cause changes in the pharmacological response of the drug target organ, without affecting the kinetics of the drug. One drug affects the actions of another drug, causing synergism or antagonism that may involve changes in its efficacy or toxicity, and adjusting doses accordingly [6].

The most important object drugs involved in either PK or PD interactions are those with a low therapeutic index; thus, minor changes in drug concentrations or effects matter more. Also due to patient characteristics, there may be a wide interindividual variability i.e., genetic polymorphisms, renal or hepatic impairment, and even intraindividual variability [2]. Information on DDIs should always be interpreted within the clinical context.

This article aims to conduct a narrative review focusing on the major clinically significant PK DDI that can be seen in patients receiving treatment for bacterial infections. This review will neither deeply cover PD DDI nor PK DDI with other antimicrobials like antiviral, antimalarial, or anti-protozoal drugs.

MATERIAL AND METHODS

Data Sources. A Pubmed search was conducted in July 2023 with the following MeSH terms ("Anti-Bacterial Agents" [Pharmacological Action]) AND "Drug Interactions"[Mesh] that retrieved 19153 results. After limiting article type to clinical trial or meta-analysis or randomized controlled trial or review or systematic review, publication date last 5 years, species: humans and language: English, French or Spanish, 191 results remained, that were manually examined to the final selection of 80 articles. We also reviewed the book by Pai MP, et al. Drug Interactions in Infectious Diseases, nice reviews previously performed, as well as UpToDate and product package inserts/summary of product characteristics (SPC) of new antimicrobials [4,6–8].

Selection Criteria for the Major Interactions. After a review of the literature on PK DDI with the major antibiotic families, the drugs most associated with these interactions were determined. Being a very broad topic, the review was limited to commonly used drugs.

PK DDIs were graded according to UpToDate database as major (classified as "X" -avoid combination- or "D" -consider treatment modification-); moderate (C –monitor therapy) or minor (B –no action needed-) according to clinical significance. In some cases, the summary of product characteristics of the drug was also consulted.

Drugs in each antibacterial were organized by numbers in different sections, while interactive drugs appeared in order of relevance.

KEY CONTENT AND FINDINGS

Each of the four basic processes that determine the PK behavior of a drug- absorption, distribution, metabolism, and excretion- may be affected by other drugs. In the past, major focus was on distribution, particularly plasma protein binding, but nowadays it has been proved that the main cause of DDI is the modulation of the activity (inhibition or induction) of enzymes and transporters. The mechanisms involved in the most important PK interactions are described below.

Pharmacokinetic drug-drug interactions mechanisms

1. Absorption

Gastric pH may change the solubility or the chemical stability of some oral antimicrobials, notably certain azole antifungals (i.e., posaconazole, itraconazole, ketoconazole) and beta-lactam antibiotics (i.e., cefuroxime). The oral bioavailability of these drugs may be modified by proton pump inhibitors or H2-receptor antagonist therapy [4]. Cationic antacids (especially magnesium or aluminum but also, to a lesser degree, calcium, and iron), sucralfate (sucrose aluminum sulfonate), or perhaps kaolin-pectin form insoluble chelates with certain antibiotics including tetracyclines, fluoroquinolones, and maybe lincosamides, reducing the absorption of the antibiotic. Regarding coadministration with meals, some antimicrobial drugs may be taken with or without meals (i.e., acyclovir, azithromycin, amantadine, ciprofloxacin, famciclovir, fluconazole, flucytosine, isavuconazole, levofloxacin, linezolid –avoid foods rich in tyramine and caffeine-, moxifloxacin, oseltamivir, posaconazole tablets, rifabutin, pyrazinamide, valacyclovir). Levofloxacin and moxifloxacin can be taken with milk while administration of ciprofloxacin with milk should be avoided. Conversely, other drugs must be taken with an empty stomach –1 hour before or 1 hour after meals- (i.e., isoniazid, , rifampin). Lastly, sometimes it is preferred to take them with food to improve absorption (i.e., atovaquone, ribavirin, rifapentine, valganciclovir) or for gastrointestinal tolerability reasons (i.e., amoxicillin-clavulanate, cephalosporins, clarithromycin, clindamycin, doxycycline, trimethoprim-sulfamethoxazole, ethambutol, famciclovir, metronidazole -avoid ethanol-) [4,9].

2. Metabolism

Metabolism is a biotransformation process, where endogenous and exogenous compounds are converted to more polar products to ease their elimination from the body. The process of metabolism is divided into 3 phases. Phase I metabolism involves functionalization reactions. Phase II drug metabolism is a conjugation reaction. Phase III refers to transporter-mediat-

Table 1 **Weak, moderate or strong inhibitors or inducers of the main enzymes of Cytochrome P-450. Main substrates of the affected enzymes (adapted from to UpToDate). [42,140]**

CYP 1A2			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Ciprofloxacin	**Moderate inducers** None	Agomelatine, Alosetron, Caffeine, Clomipramine, Clozapine, Duloxetine, Melatonin, Olanzapine	Pirfenidone, Propranolol, Rasagiline, Ropinirole, Ropivacaine, Theophylline, Tizanidine
Weak inhibitors Acyclovir, Glecaprevir & pibrentasvir, Valacyclovir	**Weak inducers** Rifampin		
CYP 2B6			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors None	**Moderate inducers** Efavirenz , Nevirapine, Rifampin (rifampicin) , Ritonavir	Bupropion , Cyclophosphamide , Efavirenz , Ifosfamide , Methadone	
Weak inhibitors None	**Weak inducers** Isavuconazole		
CYP 2C8			
Strong inhibitors None	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderate inhibitors Sulfamethoxazole & trimetoprim	**Moderate inducers** None	Apalutamide, Dabrafenib, Enzalutamide, Ozanimod, Paclitaxel, Pioglitazone	Repaglinide, Rosiglitazone, Selexipag, Tucatinib, Velpatasvir
Weak inhibitors Favipiravir, Tecovirimat, Trimetoprim	**Weak inducers** None		
CYP 2C9			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Fluconazole, Sulfamethoxazole & trimetoprim	**Moderate inducers** Rifampin (rifampicin)	Acenocumarol, Celecoxib, Diclofenac, Etravirine, Flurbiprofen, Fluvastatin, Glyburide, (glibenclamide), Gliclazide, Glimepiride	Lesinurad, Losartan, (active metabolite), Meloxicam, Nateglinide, Phenytoin, Siponimod, Sulfamethoxazol, & trimetoprim, Tolbutamide, Warfarin
Weak inhibitors Voriconazole	Weakinducers Rifabutin		
CYP 2C19			
Strong inhibitors Fluconazole	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderateinhibitors Voriconazole	Moderateinducers None	Carisoprodol, Cilostazol, Citalopram, Clobazam, Clopidogrel (prodrug), Diazepam, Escitalopram, Esomeprazole	Etravirine, Fosphenytoin, Lansoprazole, Methadone, Omeprazole, Pantoprazol, Phenytoin, Voriconazole
Weakinhibitors Etravirine, Tecovirimat	**Weak inducers** Efavirenz		
CYP 2D6			
Strong inhibitors Quinidine	**Inducers** None	**Main substrates**	
Moderate inhibitors Darunavir , Terbinafine (systemic)		Amitriptyline, Aripiprazole, Atomoxetine, Carvedilol, Clomipramine, Codeine (prodrug), Desipramine, Dextromethorphan, Duloxetine, Eliglustat, Flecainide, Haloperidol, Imipramine, Lisdexanfetamine, Metoclopramide, Metoprolol, Mexiletine	Nebivolol, Nortriptilyne, Paroxetine, Perphenazine, Pimozide, Propafenone, Propranolol, Risperidone, Rucaparib, Sertindole, Tamoxifen (prodrug), Tamsulosine, Tetrabenazine, Tramadol (prodrug), Vortioxetine, Zuclopenthixol
Weak inhibitors Chloroquine , Cobicistat			

Table 1 **Weak, moderate or strong inhibitors or inducers of the main enzymes of Cytochrome P-450. Main substrates of the affected enzymes (adapted from to UpToDate). [42,140] (cont.)**

CYP 2E1			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Isoniazid	**Moderate inducers** None	Acetaminophen, Chlorzoxazone	
Weak inhibitors	**Weak inducers** Isoniazid		
CYP 3A4			
Strong inhibitors Atazanavir (boosted*), Clarithromycin, Cobicistat, Darunavir (boosted*), Elvitegravir &tcobicistat, Fosamprenavir &tritonavir, Itraconazole, Ketoconazole, Levoketoconazole, Lopinavir, &ritonavir, Nirmatrelvir &tritonavir, Posaconazole, Ritonavir, Tipranavir &tritonavir, Voriconazole	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderate inhibitors Clofazimine, Erythromycin, Fluconazole, Fosamprenavir, Isavuconazole, (isavuconazonium sulfate) , Lefamulin, Letermovir	**Moderate inducers** Efavirenz, Etravirine, Nafcillin, Rifabutin, Rifapentine	Abemacxiclib, Alfentanil, Alfuzosin, Alprazolam, Amiodarone, Amlodipine, Apixaban, Aprepitant, Artemeter, &lumefantrine, Atorvastatin, Avanafil, Bedaquiline, Bosutinib, Budesonide, Buspirone, Carbamazepine, Ciclesonide, Cilostazol, Clarithromycin, Clindamycin, Clozapine, Cobicistat, Cobimetinib, Colchicine, Conivaptan, Crizorinib, Cyclosporine, Dabrafenib, Dapsone, Darunavir, Dasatinib, Delamanid, Dihydroergotamine, Disopyramide, Domperidone, Doravirine, Doxorubicin, Dronedarone, Efavirenz, Elbasvir, &tgrazoprevir, Eletriptan, Elvitegravir, Encorafenib, Entrectinib, Eplerenone, Eravacycline, Ergotamine, Erlotinib, Etravirine, Erythromycin, Etravirine, Everolimus, Felodipine, Fentanyl, Fluticasone, Fosamprenavir, Fosaprepitant, Fostematinib, Fostemsavir, Glecaprevir&tpibrentasvir, Hydrocodone, Ibrexafungerp, Ibrutinib, Iinotecan, Isavuconazole, Itraconazole, Ivabradine, Ivacaftor, Ivosidenib	Lapatinib, Lefamulin, Lercanidipine, Lopinavir, Lovastatin, Lumacaftor/ivacaftor, Lurasidone, Macitentan, Maraviroc, Maribavir, Mefloquine, Methadone, Methylergometrine, Midazolam, Midostaurine, Mitotane, Naldemedine, Naloxegol, Neratinib, Nevirapine, Nifedipine, Nilotinib, Nimodipine, Nirmatrelvir, Nisoldipine, Olaparib, Ombitasvir,, paritaprevir, ritonavir, plus dasabuvir, Oxycodone, Palbociclib, Pazopanib, Pimozide, Praziquantel, Pretomanid, Quetiapine, Quinine, Quinidine, Ranolazine, Regorafenib, Ribociclib, Rifabutin, Rilpivirine, Rivaroxaban, Rolapitant, Salmeterol, Sertindole, Sildenafil, Silodosin, Simeprevir, Simvastatin, Sirolimus, Sonidegid, Sorafenib, Sunitinib, Tacrolimus, Temsirolimus, Tezacaftor/Ivacaftor, Ticagrelor, Tofacitinib, Tolterodine, Tolvaptan, Toramifene, Trazodone, Triazolam, Upadacitinib, Vandetanib, Vardenafil, Velpatasvir, Venetoclax, Vincristine, Voriconazole, Zanubrutinib
Weak inhibitors Azithromycin, Ciprofloxacin, Clotrimazole, Elbasvir&tgrazoprevir, Glecaprevir&tpibrentasvirIsoniazid, Quinidine	**Weak inducers** Disopyramide Flucloxacillin Nervirapine		

***Boosted with cobicistat or ritonavir. Inhibitors and inducers of an enzyme (perpetrators of DDI) can alter serum concentrations of drugs that are dependent upon that enzyme for their metabolism (victims of DDI). Clinically significant interactions can occasionally occur due to weak inhibitors and inducers when they are combined with a drug that has a narrow therapeutic index and is highly dependent on that enzyme for its metabolism. Accordingly, specific interactions should be checked in the Package insert or using a drug interaction database.**

ed elimination of drug and/or metabolites from body normally via liver, gut, kidney, or lung [10,11].

The most common phase I drug-metabolizing enzymes are represented by CYP450 (CYP) superfamily. CYP enzymes are distributed throughout various tissues and organs, of which the liver and small intestine are the major contributors to the overall metabolism and elimination of drugs. The alteration of CYP activities can occur by three main mechanisms: reversible inhibition, mechanism-based inactivation (including quasi-irreversible and irreversible inhibition), and induction. Table 1 presents antimicrobials that act as weak, moderate or strong inhibitors or inducers of the main enzymes of CYP and main substrates of the affected enzymes. Genetic polymorphisms and epigenetic changes in CYP genes may be responsible for

inter-individual and interethnic variations in disease susceptibility and the therapeutic efficacy of drugs [10]. The result of a PK DDI may vary if the victim is a prodrug activated through an enzyme that is inhibited by another drug, so the inhibitor may decrease its efficacy. Similarly, an inducer may increase the toxicity of the drug. If the drug has toxic metabolites, an inducer of that metabolic pathway may increase its toxicity.

CYP enzymes can be transcriptionally activated by various xenobiotics and endogenous substrates through receptor-dependent mechanisms leading to enzyme induction. Reversible inhibition refers to competition of two drugs for a CYP. Mechanism-based inhibition of a CYP involves the inactivation of the enzyme through the formation of metabolic intermediates that bind tightly and irreversibly to the enzyme. Therefore, metabolic DDI that arise through mechanism-based inactivation of CYPs can be more severe and long lasting than reversible inhibition. Among antimicrobials, clinically important mechanism based CYP3A4 inhibitors include macrolide antibiotics (i.e., clarithromycin and erythromycin), and anti-HIV agents (i.e., ritonavir and cobicistat) [12].

When we are faced with a DDI, one of the important points to be considered is time-dependent recovery of altered enzyme activity after discontinuation of causative drugs. The time to wait must be sufficient to avoid the carry-over effect of the preceding treatment. Imai H et al. reviewed studies conducted in humans about this topic [13]. In the case of competitive inhibition, time-dependent changes of metabolic capacity are thought to depend on time to elimination (half-life) of the inhibitors themselves. On the other hand, de novo enzyme synthesis is thought to be the rate-controlling factor in mechanism-based enzyme inhibition. The recovery half-lives after mechanism-based inhibition are about 20–50 h. From these data, it is estimated that 90% or more recovery can be achieved 10 days after discontinuation of mechanism-based inhibitors. Regarding enzyme induction, the recovery process is thought to be a composite phenomenon of the residual signaling effects of induction (regulated mainly by nuclear receptors) and enzyme degradation, which is considered the dominant recovery process. The recovery half-lives are approximately 40–60 h after enzyme induction. It is estimated that 90% or more recovery can be achieved 14 days after discontinuation of an inducer. Genetic polymorphisms and CYP families involved could also influence enzyme recovery.

For patients treated concurrently with enzyme inhibitors or inducers and drugs that have a narrow therapeutic range (i.e., a slight reduction in its concentrations causes a loss of efficacy or a small increase causes toxicity, like tacrolimus), careful monitoring is advised during those periods [13].

During phase II drug metabolism, the drugs or metabolites from phase I pathways are enzymatically conjugated with a hydrophilic endogenous compound with the help of transferase enzymes [10]. Glucuronidation is the major phase II drug metabolism pathway and UDP-glucuronosyltransferases (UGTs) the main implicated enzymes [10]. UGT1A1 is the highly expressed phase II enzyme in human, which preferentially metabolizes bilirubin. UGTs are normally highly expressed in the liver and gut. Rifampin is a well-known inducer of the expression of UGTs and decreases exposure of substrates (victim drugs). On the other hand, competition for UGTs may lead to inhibition of metabolism and increased drug exposure.

Transporters (Phase III pathway) are important determinants of drug disposition and response. They are present in many locations, such as liver, kidney, intestine, and brain. Conceptually, uptake transporters help in transferring the molecules into the cells and efflux transporters pump them outside the cell. They are classified into 2 main superfamilies: ATP-binding cassette (ABC) and solute carrier (SLC) transporters. ABC transporters are dependent on the energy (ATP) consumption. Information on substrates, inhibitors and DDI of the main transporters can be found on the website UCSF-FDA TransPortal [14].

3. Renal Excretion

Interference with renal excretion of drugs can cause drug interaction by competition for renal tubular secretion or by altered tubular reabsorption. Renal tubular secretion is generally mediated by a coordinate activity of transporter-mediated uptake across the basolateral membrane of proximal tubular cells by OCT2 and of transporter-mediated export across the luminal membrane by multidrug and toxin extrusion 1 and 2-K (MATE1/MATE2-K). Renal transporter-mediated drug interactions tend to be more modest compared to those mediated by hepatic transporters. Trimethoprim increased metformin AUC by 1.3 to 1.4-fold. Another example is the mandatory use of probenecid to prevent cidofovir nephrotoxicity. Cidofovir renal cytotoxic effects are determined by the uptake transporter organic anion transporter 1 (OAT1) and probenecid is an OAT inhibitor [15].

NARRATIVE REVIEW FINDINGS. MAIN PHARMACOKINETIC DRUG-DRUG INTERACTIONS AFFECTING ANTIBACTERIAL AGENTS

For interactions to be clinically significant, the magnitude of the interaction must be sufficient to affect clinical outcomes, that is, efficacy or toxicity. This is usually the case when the interaction is large in magnitude or the drug victim of the interaction has a narrow therapeutic margin. Several drugs have a pronounced concentration-response relationship and a narrow therapeutic margin. In these cases, drug interactions can cause serious problems, for example, antithrombotic agents, antiarrhythmics, antiepileptics, lithium, and with various antineoplastic and immunosuppressive drugs [16]. Clinically relevant PK interactions are described below.

Information on DDI is often limited, usually from studies in healthy volunteers or clinical cases [17]. Therefore, it is important to report adverse drug reactions (ADR) to the surveillance programs of the respective countries, especially if the toxicity is severe or previously unknown or occurs with newly marketed antimicrobials.

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics are a relatively old group of antimicrobials, which became one of the most widely used due to their broad antimicrobial spectrum and wide therapeutic index. Their introduction from the 1930s onwards completely changed the fight against bacterial infectious diseases [18].

Although these drugs are widely used in daily practice, reports on interactions are scarce and often of minor importance. Most knowledge of interactions with other treatments has been obtained from clinical cases, as there are few prospective studies examining potential interactions. The most often described potential interactions are induction of the CYP3A4 enzyme by flucloxacillin (weak inducer) and/or nafcillin (moderate inducer), effect on intestinal flora, effect on renal clearance (i.e., if the co-administered drug has a higher affinity for the renal transporter, a decrease in tubular excretion of the antibiotic will be seen) and possible decreased plasma protein binding of the drug [6,7,19].

Cefiderocol is a new type of cephalosporin, a catechol-substituted siderophore, similar in structure to cefepime and ceftazidime. In laboratory studies, it has been observed that cefiderocol triggers the activity of CYP3A4. The drug's product information states that it could potentially lower the effectiveness of systemic hormonal contraceptives. Therefore, it's advisable to use an additional contraceptive method while undergoing treatment with cefiderocol and continue this precaution for up to 28 days after the treatment ends. Since cefiderocol's induction of CYP3A4 occurs through a process involving PXR, it might also affect other proteins activated by PXR, such as the CYP2C family and P-gp. However, there's limited information available regarding its practical significance in clinical settings [20].

The major pharmacokinetic interactions of beta-lactams are described as follows:

1. Valproic Acid and Derivatives. (major)

Several retrospective studies of patients receiving valproate proved that plasma levels of this drug decreased when carbapenem antibiotics were added to valproate. Multiple case series conclude that this decrease is significant, greater than 90% [21]. Chai PY et al. conducted a systematic review and meta-analysis until July 2020. The overall increased seizure frequency, expressed as median value and range, amounted to 26.3% (3.85%–100%) during combination treatment although this could also be due in part to the presence of carbapenems (especially imipenem) to which an increased risk of seizures has been attributed. This DDI does not seem to be dose dependent as no difference was found in mean serum valproate concentration between the different doses of valproate or carbapenem during combination treatment. The onset of serum valproate decrease was within one to three days following carbapenem initiation, with the lowest values occurring after 4 to 11 days, and slowly increased to similar pre-carbapenem level within 1 to 2 weeks after carbapenem discontinuation. This interaction was common to all carbapenem antibiotics and could not be reversed by increasing the dose of valproate [21–23].

The specific mechanism responsible for this interaction is not completely understood. Suzuki E et al. investigated it in chimeric mice with humanized livers. Their results strongly support that the interaction is caused by a long-lasting inhibition of hepatic acyl-peptide hydrolase. This enzyme mediates the hydrolysis of valproic acid-glucuronide to regenerate the valproic acid. After co-administration, a more rapid decrease in plasma valproic acid concentration than without carbapenems was seen together with an increase in plasma AUC and urinary excretion of valproic acid-glucuronide. Acyl-peptide hydrolase was strongly inhibited even at 24 h after co-administration of meropenem and valproic acid to the chimeric mice [24].

2. Calcium salts. (major)

As indicated in ceftriaxone SPC, the coadministration of an intravenous infusion of calcium with this antibiotic is contraindicated in neonates less than 28 days old. This contraindication appears as a result of several series of neonatal patients who developed lithiasis due to the presence of calcium precipitates in kidney, lungs or liver. Normally, the liver eliminates a considerable proportion of ceftriaxone in the form of soluble salt. However, ceftriaxone is an anion and, when drug concentrations are high, these anions can bind to calcium ions to form insoluble complexes that precipitate in the biliary system. It appears that stones can form in the same way in the renal collecting system. In a pediatric study, 7.8% of the population was found to have ultrasonographically identified nephrolithiasis, all patients had received normal or high doses of ceftriaxone and had had creatinine, urea and calcium levels unchanged from previous values. In non-neonatal patients, ceftriaxone and calcium-containing intravenous solutions can be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid [25,26].

3. Vitamin K Antagonists. (moderate)

When penicillins are concurrently used with vitamin K antagonists, the anticoagulant effect may be potentiated. Monitor for increased INR and for signs of bleeding when initiating a penicillin or cephalosporin, and for INR decrease when discontinuing, including several days after cessation [27].

Although some studies did not detect a change in the INR value in patients treated with warfarin and amoxicillin-clavulanic acid, a large case-control study assessed the increased risk of bleeding in patients chronically treated with vitamin K antagonist who had amoxicillin/clavulanic acid added for infection [28]. The results showed a 3-point increase in the odds ratio for serious bleeding [29].

The possible mechanism of this interaction is not clear but could be related to the eradication of microorganisms in the intestine that produce vitamin K precursors [30]. This depletion of vitamin K stores results in hypoprothrombinemia, even without concomitant treatment with vitamin K antagonists. Although this mechanism is mainly due to PD DDI, alternative

PK mechanisms have been suggested, such as preferential hepatic metabolism of clavulanic acid over warfarin, enhancing the concentrations of the second drug and, consequently, increasing INR. Semisynthetic cephalosporins having a methylthiotetrazole substituent at the 3-position, such as cefoperazone and cefotetan, have been associated with the development of hypoprothrombinemia [29–31]. In contrast, an opposite effect was seen with the concomitant use of warfarin, dicloxacillin, and nafcillin, which resulted in a decreased INR [32].

4. Methotexate. (moderate)

The interaction between cephalosporins, penicillins and methotrexate, leading to an accumulation of methotrexate in the blood, and increased toxicity, has been widely described in several clinical cases of onco-hematologic patients, especially with the simultaneous use of piperacillin-tazobactam [33].

Although the causative mechanisms of this interaction are not clear, some authors propose competition for the organic anion transporter 3 (OAT3). Methotrexate is mainly eliminated by the kidneys through OAT1 and OAT3, whereas most of the penicillins and cephalosporins are also substrates of these carriers (Table 2). Another potential mechanism of interaction is the displacement of methotrexate from serum proteins by cephalosporins (i.e., ceftriaxone), leading to an increase in unbound serum methotrexate, which may result in toxicity [34,35]. Patients receiving penicillins during methotrexate therapy should be closely followed to avoid severe toxicity [35]. Meropenem seems to be a safer alternative in patients treated with high-dose methotrexate [36].

5. Probenecid. (moderate)

Probenecid is a uricosuric and renal tubular blocking agent that inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by any route the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins [37]. Some beta-lactams SPC recommend against its use.

Most of the penicillins and cephalosporines, as well as avibactam are substrates of OAT1 and OAT3 transporters that might contribute to its active uptake from the blood compartment and, therefore, affect its excretion. When co-administered with probenecid, studies have shown a decreased renal excretion and increase in AUC of amoxicillin and ampicillin, cefotaxime and meropenem between 50-100%, 80-100%, and 56% respectively [38,39]. Probenecid inhibited avibactam uptake by 56% to 70% in vitro [40].

Clinical relevant DDIs with beta-lactams are summarized in table 3.

MACROLIDES

Macrolide antibiotics are used in the treatment of a variety of infections. Erythromycin is the older macrolide and, by structural modifications, derivates such as azithromycin and clarithromycin have appeared.

Azithromycin and clarithromycin have a broader spectrum of activity including atypical, mycobacterial organisms and selected gram-negative, as well as gram-positive organisms.

Macrolide antibiotics have a variety of PK DDI, which are mostly mediated by the inhibition of hepatic cytochrome CYP3A enzymes. Azithromycin is a weak inhibitor of CYP3A4 while erythromycin is a moderate inhibitor and clarithromycin is a strong inhibitor (Table 1). Even though azithromycin is only a weak CYP3A4 inhibitor is not entirely free of risk due to its inhibition of the P-gp [41]. Clarithromycin and erythromycin are strong inhibitors of P-gp (Table 2).

On the other hand, macrolide antibiotics have a high risk of prolonging the QTc interval. These PD DDI may be reviewed elsewhere [42,43].

The most frequent interactions of macrolide antibiotics are summarized as follows:

1. Statins. (major)

Macrolides inhibits the enzymatic activity of CYP3A4 which plays a role in the metabolism of statins that are CYP3A4 substrates. Co-administration macrolides with statins that are primarily metabolized by CYP3A4, especially simvastatin and lovastatin, may lead to increased serum concentrations of those drugs and increased risk for statin-related adverse reactions, including myopathy and rhabdomyolysis. According to FDA prescribing information, concomitant use of simvastatin / lovastatin and clarithromycin / erythromycin is contraindicated [44,45].

Patel AM et. al evaluated the concomitant administration of clarithromycin or erythromycin with statins, which was associated with a higher risk of adverse events compared with statins alone. [44] Clarithromycin increased the exposition (AUC) of atorvastatin 3.5-fold its original value, and erythromycin increased it by 1.3-fold meanwhile azithromycin had no impact on atorvastatin exposure. Simvastatin is not recommended for co-administration with clarithromycin and erythromycin because of an increase of 11-fold and 4-fold of its AUC, respectively compared with basal values. A similar increase is expected with lovastatin [45–47]. Erythromycin also increased 3-fold the pitavastatin AUC, so the manufacturer recommends not to exceed the dose of 1 mg a day if co-administered [47]. As pitavastatin lacksof appreciable CYP3A4 metabolism, this interaction seems mainly due to transporter mediated PK DDI. Rosuvastatin and fluvastatin are less affected by CYP3A4 inhibition and azithromycin is a weak CYP3A4 inhibitor. These drugs can be considered safer alternatives [46].

2. Immunosuppresants. (major)

Macrolide antibiotics decrease the metabolism of calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus [48]. Concomitant treatment of clarithromycin and erythromycin with CNI or mTOR inhibitors results in a significant increase of immunosuppressant AUC and Cmax (3-10-fold). A 50% dose reduction is recommended if the

Table 2 **Antimicrobials as substrates, inhibitors, and inducers of the main drug transporters. (Modified from to UpToDate). [41,42,120]**

Inhibitors	Inducers	Substrates	
P-glycoprotein [P-gp] or multidrug resistance protein 1 (MDR1)			
Azithromycin	Rifampin (rifampicin)	Ciprofloxacin (minor)	Lefamulin (major)
Clarithromycin (strong)		Delafloxacin (minor)	Omadacycline (minor)
Erythromycin (strong)		Erythromycin (minor)	Quinidine (minor)
		Fidaxomicin (minor)	Rifampin (rifampicin) (minor)
			Rifaximin (major)
BCRP Breast Cancer Receptor Protein [ABCG2]			
Tedizolid	Rifampin (rifampicin)	Delafloxacin	
OAT1/3 organic anion transporters 1 and 3 [SLC22A6]/[SLC22A8]			
None	None	Amoxicillin	Ciprofloxacin
		Ampicillin	Cloxacillin
		Avibactam	Ertapenem
		Cefaclor	Levofloxacin
		Cefadroxil	Meropenem
		Cephalexin	Norfloxacin
		Cefazolin	Penicillin G; Penicillin V
		Cefditoren	Piperacillin
		Cefixime	
		Cefotaxime	
		Cefoxitin	
		Ceftibuten	
		Ceftobiprole	
		Cefuroxime	
OATP1A2 organic anion-transporting polypeptides (SLCO1A2)			
Rifaximin	None	Levofloxacin	
		Rifaximin	
OATP1B1 organic anion-transporting polypeptides (SLCO1B1)			
Clarithromycin	Rifampin (rifampicin)	Rifampin (rifampicin)	
Fusidic acid		Rifaximin	
Rifampin (rifampicin) single dose			
OATP1B3 organic anion-transporting polypeptides (SLCO1B3)			
Clarithromycin	Rifampin (rifampicin)	Rifaximin	
Fusidic acid		Rifampin (rifampicin)	
Rifampin (rifampicin) single dose			
OCT1 - organic cation transporter 1 (SLC22A1)			
Trimethoprim	None	Ethambutol	
OCT2 - organic cation transporter 2 [SLC22A2]			
Trimethoprim	None	Ethambutol	

Table 3 Summary of clinical relevants DDIs with beta-lactams.

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Valproic acid	Major	Significant decrease, greater than 90% of valproate serum concentration, probably caused by a long-lasting inhibition of hepatic acyl-peptide hydrolase	Valproate serum concentration	[22,24]
Calcium salts	Major	Coadministration of an intravenous infusion of calcium with ceftriaxone is contraindicated in neonates less than 28 days old, due to the presence of calcium precipitates in kidney, lungs or liver.		[25]
Warfarin	Moderate	When penicillins are concurrently used with vitamin K antagonists, the anticoagulant effect may be potentiated. It could be related to the eradication of microorganisms in the intestine that produce vitamin K precursors. With dicloxacillin, and nafcilliun the opposite effect may occur.		[29]
Methotrexate	Moderate	Cephalosporins and penicillins (especially piperacillin/tazobactam) reduce the elimination of methotrexate by competition for the organic anion transporter 3 (OAT3). Meropenem seems to be a safe alternative.	MTX Cl MTX serum concentration	[33,34]
Probenecid	Moderate	Inhibition of the tubular secretion of penicillin and increase of plasma levels. co-administered with probenecid, studies have shown a decreased renal excretion and increase in AUC of amoxicillin and ampicillin, cefotaxime and meropenem.	50-100% AUC	[38,39]

AUC: area under the curve; DDI: drug-drug interaction; MTX: methotrexate; PK: pharmacokinetics.

combination is used, and daily drug concentration monitoring [49]. There are several case reports of toxicity of CNI and mTOR inhibitors due to administration with clarithromycin. As an example, Cheung et al. described supratherapeutic blood concentrations of tacrolimus due to concomitant use with clarithromycin, which was effectively managed by stopping the macrolide administration and reducing tacrolimus dose. It is recommended to monitor blood concentrations [49–51]. Azithromycin is an inhibitor of P-gp. However, the DDIs between CNI or mTOR inhibitors and azithromycin are mild and no a priori dose adjustment of immunosuppressants is necessary [49].

3. Benzodiazepines. (major)

The serum concentration of midazolam and triazolam may increase when combined with clarithromycin/ erythromycin, as well as the risk and severity of adverse effects (Table 4). Intestinal and hepatic CYP3A4 inhibition by clarithromycin significantly reduced the clearance of midazolam in the elderly. Clarithromycin administration led to an increase in the AUC of midazolam by 3.2-fold following intravenous dosing and 8.0-fold following oral dosing. This is due to the intestinal first-pass effect of midazolam [52].

Alprazolam co-administered with clarithromycin may increase benzodiazepine exposure. Gao X et al. reported a case of lethargy, short-term memory loss, and limb weakness in an older patient in treatment with alprazolam and clarithromycin [53]. Alprazolam AUC also increased 61% when co-administered with erythromycin [54].

4. Other drugs. (major)

Table 4 shows the drugs that should be avoided with a potent CYP3A4 inhibitor due to the risk of increased toxicity, especially if the antimicrobial is prescribed for an extended period [42,43].

5. Digoxin. (moderate)

The serum concentration of digoxin can be increased when it is combined with macrolides. The FDA SPC for digoxin and other resources indicate that macrolides may potentiate digoxin toxicity [55]. The inhibition of the P-gp transporter in the intestine is the likely mechanism of this interaction, as digoxin is a P-gp substrate, and the macrolides may inhibit this transporter.

The increase in digoxin concentrations after an oral dose of 400 mg of clarithromycin is approximately 70%. Gomes T et al. published a population-based PK study in which treatment with clarithromycin, erythromycin, and azithromycin was associated with digoxin toxicity in older people. The risk of digoxin toxicity was found to be higher with clarithromycin than with erythromycin or azithromycin [56,57]. Physicians should recognize this interaction when making prescribing decisions and should consider the use of an alternative when appropriate according to the patient's situation.

6. Ketamine. (moderate)

Ketamine is extensively metabolized in the liver by cytochrome CYP 3A4, 2B6, and 2C9 enzymes. Macrolide antibiotics such as clarithromycin and erythromycin may increase ketamine exposure, particularly in its oral form. After oral administration of ketamine, clarithromycin increased the Cmax of ketamine by 3.6-fold and the AUC by 2.6-fold. This effect is reflected in a high incidence of adverse reactions, so monitoring is recommended [58].

Clinical relevant DDIs with macrolides are summarized in table 5.

Table 4 **Drugs that should be avoided with strong CP3A4/P-gp inhibitors (this list is not exhaustive) [42,43].**

Drugs that are sensitive substrates of CYP3A4 and/or P-gp.	
Abemaciclib	Lurasidone
Alfuzosin	Methylergometrine
Amiodarone	Midazolam (oral)
Aliskiren	Midostaurin
Apixaban	Mitotane
Avanafil	Mometasone*
Bosutinib	Naloxegol
Budesonide (inhaled) *	Nilotinib
Ciclesonide (inhaled) *	Olaparib
Clozapine	Ombitasvir/paritaprevir/ritonavir/dasabuvir
Cobimetinib	Palbociclib
Crizotinib	Pazopanib
Dabrafenib	Pimozide
Colchicine	Quetiapine
Dasatinib	Quinidine
Dihydroergotamine	Ranolazone
Disopyramide	Regorafenib
Domperidone	Ribociclib
Dronedarone	Rivaroxaban
Eletriptan	Salmeterol
Eplerenone	Sertindole
Everolimus	Sildenafil (high dose - pulmonary hypertension)
Fentanyl	Silodosin
Flecainide	Simeprevir
Fluticasone	Simvastatin
Ibrutinib	Sunitinib
Irinotecan	Temsirolimus
Ivabradine	Ticagrelor
Lapatinib	Tolterodine
Lercanidipine	Triamcinolone (systemic)
Lovastatin	Triazolam
Lumacaftor/ivacaftor	

*** Increased systemic exposure and an increased risk of corticosteroid related adverse events. The longer the duration of antimicrobial therapy, the greater the risk (probably minimal risk with 5-7 days). In most cases the toxicity occurred after 3 months or more, even years. Nevertheless, there are also some cases after a brief time (2-3 weeks) with fluticasone and boosted protease inhibitors which are strong inhibitors of CYP3A4. It is recommended if it is possible to use beclomethasone [141,142].**

FLUOROQUINOLONES

Fluoroquinolones are antimicrobial agents used for the treatment of a wide range of bacterial infections [6].

The most often described potential interactions are related to absorption (chelation) or metabolism (ciprofloxacin is a is a moderate inhibitor of CYP1A2; see Table 1). See additional information in the SPC.

1. Divalent or trivalent cations. (moderate-major depending on the drug pair)

Concomitant administration of enteral quinolones with divalent or trivalent cation-containing compounds results in a reduction in quinolones bioavailability. The mechanism that is believed to cause decreased absorption is the formation of insoluble complexes or chelators in the digestive tract [59]. When phosphate-binders are administered concomitantly with a quinolone, reduced absorption occurs due to chelation caused by phosphate binders, demonstrated by a reduction of the Cmax and AUC. This likely results in decreased therapeutic efficacy of quinolone therapy [60].

Studies have found that the absorption of ciprofloxacin is the most affected when it is administered with cations, particularly aluminum, magnesium, or sucralfate, in contrast to levofloxacin which is the quinolone least affected by this interaction. Oral ciprofloxacin-multivalent cation interactions studies found alterations in ciprofloxacin absorption PK parameters when administered simultaneously with aluminum/magnesium (-84 to -91% AUC), sucralfate (-88% AUC), iron (-42 to -67% AUC), calcium (-29 to -42% AUC), zinc (-22% AUC), or multivitamins with minerals [61]. Ciprofloxacin should not be taken with milk or other calcium supplemented foods or beverages [62].

Aluminum, magnesium, and iron reduced the AUC of levofloxacin by 44%, 22%, and 19%, respectively. Moxifloxacin AUC was reduced about 60% by aluminum and magnesium, and 30% by iron. Calcium did not significantly affect levofloxacin or moxifloxacin AUC. Therefore, they can be taken with milk.

The interaction with antacids is higher when they are taken shortly before the quinolone (within 2 h prior) and is probably of not clinical relevance if the antacid is taken more than 2 h apart from the antibiotic [63].

2. Clozapine. (major)

Clozapine is an atypical antipsychotic that is metabolized by the CYP1A2 enzyme; therefore, its elimination may be altered with the concomitant use of ciprofloxacin, an inhibitor of this enzyme. Clozapine may cause myelotoxicity. A study carried out in Finland, adding 250mg of ciprofloxacin every 12h or placebo to clozapine treatment, showed that plasma levels of the antipsychotic increased by up to 29%; they recommended close monitoring of patients treated with both drugs [64]. There are multiple reports describing this interaction as well as possible adverse effects such as increased sedation, rhabdomyolysis in severe cases and even one death attributed to high clozapine concentrations [65]. In contrast, Espnes K et al., published a case report concluding that the interaction was not as pronounced as previously reported, and

Table 5 Summary of clinical relevant DDIs with macrolides

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Statins	Major	Co-administration macrolides with statins that are primarily metabolized by CYP3A4, especially simvastatin and lovastatin, may lead to increased serum concentrations of those drugs.	AUC 4 – 11 fold	[44]
Immuno-suppressants	Major	Decrease of the metabolism of calcineurin inhibitos and mTOR inhibitors by CYP3A4.	AUC 3 – 10 fold	[49,50]
BZDs	Major	Intestinal and hepatic CYP3A4 inhibition increases serum concentration of midazolam, triazolam and alprazolam.	AUC 3 – 8 fold	[54]
Digoxin	Moderate	Serum concentration of digoxin due to inhibition of the P-gp transporter.	70% digoxin serum concentration	[56]
Ketamine	Moderate	Inhibition of ketamine liver metabolism by CYP3A4. DDI particularly important when ketamine is administered in its oral form.	2.6-fold AUC 3.6-fold Cmax	[58]
Clopidogrel	Moderate	Clopidogrel is administered as a prodrug that needs to be activated by CYP, mainly CYP2C19 and CYP3A4. Erythromycin irreversibly inhibits this activation and may decrease the clopidogrel antiplatelet effect.	ADP-induced platelet aggregation	[143]
Opioid analgesics	Moderate	Some opioid analgesics like fentanyl, alfentanil, hydrocodone, and oxycodone are major substrates of cytochrome CYP3A4. A decrease in cytochrome CYP3A4 activity may impair their metabolism and increase their adverse effects.	AUC 1.3-fold	[144]
Proton Pump Inhibitors	Minor	Clarythromycin inhibits CYP3A metabolism of omeprazole.	AUC 89% of omeprazole	[145]

AUC: area under the curve; ADP: adenosine diphosphate; BZD: benzodiazepines; DDI: drug-drug interaction; PK: pharmacokinetics.

proposing that the increase in concentration suffered by the patient was a consequence of the infection [66].

As advised in SPC, it is recommended to monitor plasma levels when clozapine is used concomitantly with CYP1A2 inhibitors, as increased plasma concentrations and hence a higher frequency of adverse effects may occur. In addition, concomitant use of these two drugs may increase the risk of QT prolongation.

3. Theophylline. (major)

Theophylline is a substrate of CYP1A2. The first case reports of an interaction between quinolones and theophylline were published by Wijanands et al. and Maesen et al., who review the experience of concomitant use of theophylline with ciprofloxacin and the occurrence of adverse effects such as nausea, vomiting, and tachycardia [67,68]. Subsequently, several interaction studies have shown that ciprofloxacin 1000 mg daily, reduced theophylline clearance by 19-32% [67,69]. A case-control study in Ontario evaluated the significance of this interaction and found that the prescription of ciprofloxacin to elderly patients receiving theophylline was common and associated with a nearly two-fold increase in the risk of hospitalization for theophylline toxicity. It is plausible that increased theophylline levels could account for some of the CNS effects originally attributed to ciprofloxacin use [70,71].

The quinolones interact differently with theophylline. A meta-analysis found that ciprofloxacin and norfloxacin had a significant relevance as inhibitors of theophylline metabolism, unlike levofloxacin or moxifloxacin [6].

4. Warfarin/Acenocoumarol. (moderate)

Several studies have found a significant increase in the risk of bleeding in patients treated with warfarin and quinolones, particularly ciprofloxacin and levofloxacin. The probability varied according to time of exposure and type of quinolone. A case-control study of a cohort of elderly people evaluated the risk of bleeding with concomitant warfarin therapy with antibiotics and concluded that there was an increased risk for six antibiotic groups including quinolones [72]. In contrast, many studies of healthy volunteers have reported no change in INR or prothrombin time ratio when quinolones were added to warfarin [73].

The mechanism of this possible interaction has not been elucidated and may involve protein binding, CYP inhibition and alteration of the intestinal flora that contributes to vitamin K synthesis. An important consideration is the impact that infection may play on treatment with vitamin K antagonists. It is currently believed that substances released during inflammation and infection may cause down-regulation of some metabolic enzymes, which could interact with vitamin K antagonists and increase the risk of bleeding. Although the contribution of any of these factors is unknown, this may explain at least part of the discrepancy seen between studies of uninfected subjects and those of individuals receiving fluoroquinolones for an active infection [6].

The concluding recommendation is to monitor for increased INR and/or adverse effects of warfarin when starting quinolone therapy especially in those patients who have been on anticoagulant therapy for a long time. Even most of the studies have been done with warfarin, the same cautions should be applied to acenocoumarol due to similar characteristics [49].

5. Methotrexate. (moderate)

The concurrent administration of methotrexate and ciprofloxacin may cause increased serum concentrations of methotrexate, and therefore increase the risk of toxicity. Methotrexate toxicity can result in anemia, bone marrow suppression, and various types of infections

Several studies have reported that quinolones cause a delay in the elimination of methotrexate generating an increase in toxicity. The mechanism is unclear but is hypothesized to be related to plasma protein binding and a reduction in renal function by competitive inhibition of tubular secretion. One study measured methotrexate concentrations in patients treated with ciprofloxacin and found a delay in elimination and an increase in free methotrexate because of the competitiveness of the two drugs for binding to plasma proteins, a phenomenon already observed between methotrexate and salicylic acid [74]. Another study found that organic anion transporting polypeptides OATP1B1, OATP1B3, and OATP1A2 are involved in methotrexate transport and the last transporter also has the function of carrying levofloxacin. The exact mechanism of this interaction is unknown but may involve competitive inhibition of renal tubular secretion [75]. In addition, ciprofloxacin may interact with hepatic aldolase, the enzyme responsible for metabolizing methotrexate in the liver. Because of these potential interactions, some authors conclude that concomitant administration of these two drugs should be avoided while others recommend careful monitoring of methotrexate levels when it is administered concomitantly with ciprofloxacin and other quinolones, including levofloxacin.

6. Probenecid. (moderate)

Probenecid reduces the renal elimination of the fluoroquinolones by inhibiting their tubular secretion via competitive inhibition of renal organic ion transporters. This drug is a blocker of the renal tubular anion secretion pathway (OAT 1 and 3) and is suspected to inhibit renal clearance/excretion when co-administered with quinolones. In healthy volunteers, probenecid increased the AUC of ofloxacin and ciprofloxacin by 16% and 75%, respectively [76–78].

7. Immunosuppressants. (mild)

There are some controversies, with reports in which co-administration of ciprofloxacin and cyclosporine have caused a transient elevation of serum creatinine, while other published case reports conclude that there is no change in exposure or kinetic parameters of cyclosporine when administered concomitantly with ciprofloxacin or moxifloxacin [79]. Levofloxacin reduced the metabolism of cyclosporine increasing Cmax by 23% and AUC by 26%. It is recommended to monitor renal parameters when cyclosporin is administered with levofloxacin at higher doses (500mg every 12h) [80].

Regarding mycophenolate, it seems that quinolone antibiotics interact by killing glucuronidase-producing bacteria in the intestinal tract. Glucuronidases produced by enteric bacteria act on mycophenolic acid (MPA) glucuronide to liberate MPA, which is then available for re-absorption as part of the enterohepatic recirculation process that is suspected to contribute to up to 40% of MPA exposure. A case report describes an approximate 33% reduction in MPA AUC following introduction of intravenous ciprofloxacin to a bone marrow transplant patient receiving intravenous mycophenolate [81].

Some important PD DDI have been described with quinolones such as QTc interval prolongation, hypoglycemia, tendinitis and tendon ruptude, wich are reviewed elsewere [82].

Clinical relevant DDIs with fluoroquinolones are summarized in table 6.

RIFAMYCINS

The rifamycin antibacterial group includes rifampin, rifabutin, and rifapentine. Often, they are used for the treatment of *Mycobacterium tuberculosis*, *M. avium* complex and chronic staphylococcal infections. Rifampin in combination therapy has a significant role in the management of patients with staphylococcal endocarditis. A comparison of rifabutin and rifampin has shown that rifabutin has more activity against the *M. avium* complex and is equally potent against M. tuberculosis. This drug has awakened a considerable interest, as it affects less the hepatic metabolism and so, it has fewer interactions with other medications. Rifapentine has the advantage of presenting a long elimination half-life (14-18h) that allows the use of weekly regimens in patients with latent tuberculosis infection [83].

Rifamycins, especially rifampin, are potent inducers of the P450 enzyme complex. Rifampin is a strong inducer of CYP3A4 and 2C19, a moderate inducer of CYP2B6, 2C8, 2C9, and a weak inducer of CYP1A2. It also induces glucuronidation (UGT1A1, UGT1A9) and some drug transporters like P-gp and BCRP. A single dose of rifampin inhibits OATP1B1/1B3 and leads to a significant increase in statins exposure (i.e., 6,8-fold for atorvastatin and 127% for pravastatin have been observed with a single dose of rifamycin), whereas after multiple doses of rifampin induction phenomenon can overcome this effect and exposure (AUC) to these statines is decreased. The relative inductive potency of rifamycins towards CYP3A is rifampin > rifapentine > rifabutin. [83] CYP3A4 induction by rifapentine approaches that of rifampin (85-100%) when used daily and is more moderate when used once or twice weekly. This interaction may be delayed in onset but may persist beyond the end of treatment [83,84].

Rifamycins are eliminated by intestinal and hepatic metabolism to deacetylated, hydroxylated and formylated

Table 6 Summary of clinical relevant DDIs with fluoroquinolones.

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Clozapine	Major	Ciprofloxacin inhibits clozapine metabolism of CYP1A2 enzyme; therefore its elimination may be altered.	29% clozapine serum concentration	[64]
Theophylline	Major	Theophylline is a substrate of CYP1A2 which is inhibited by quinolones, increasing adverse effects such as nausea, vomiting and tachycardia.	29% Cl of theophylline	[67,69]
Immuno-suppressants	Moderate	Levofloxacin inhibits metabolism of cyclosporine but the mechanism is still unknown. MPA exposure may be reducted by quinolone reduction of glucuronidase producing bacteria in intestinal tract.	AUC 26%, Cmax 23% of cyclosporine. 33% AUC of MPA	[81]
Warfarin/ Acenocoumarol	Moderate	The mechanism of this possible interaction has not been elucidated and may involve protein binding, CYP inhibition and alteration of the intestinal flora that contributes to vitamin K synthesis.		[72]
Methotrexate	Moderate	Quinolones cause a delay in the elimination of methotrexate. The mechanism is hypothesized to be related to plasma protein binding and a reduction in renal function by competitive inhibition of tubular secretion.	MTX Cl MTX serum concentration	[75]
Probenecid	Moderate	Probenecid reduces the renal elimination of the fluoroquinolones by inhibiting their tubular secretion via competitive inhibition of renal organic ion transporters.	16% AUC oxafloxacin 75% AUC ciprofloxacin	[76,77]
Rifampicin	Minor	Rifampin causes a reduction in the concentration of moxifloxacin most probably because of rifampin-induced glucuronidation or sulphation.	26-32% Cmax 29-31% AUC moxifloxacin	[146]

AUC: area under the curve; Cl: clearance; DDI: drug-drug interaction; MPA: mycophenolate acid; MTX: methotrexate; PK: pharmacokinetics.

derivatives. The drugs and their metabolites are excreted in the bile and eliminated in the faeces. It is important to remember that exept for rifapentine, repeated administration of rifamycins causes an increase in their clearance due to induction of their own intestinal and/or hepatic metabolism. [85] The autoinduction of rifamycins was reported in a study by Strolin Benedetti M, et al. who found that the CYP3A subfamily is induced by either drug causing a decrease in exposure (AUC). The autoinduction of rifampin is characterized by a decrease in AUC and elimination half-life, while rifabutin only shows a decrease in AUC but no change in half-life. Steady-state conditions are generally reached after the sixth daily dose of rifampin 600 mg or rifabutin 300 mg [86].

Unlike rifampin and rifapentine, which are not metabolized by CYP, rifabutin is a mayor substrate of CYP3A4 and a minor substrate of CYP1A2. Consequently, rifabutin has a higher vulnerability to become a victim of interactions compared to the other rifamycins.

Patients receiving any rifamycin should have their medication regimen carefully analysed for DDIs. Baciewitcz AM, et al deeply reviewed rifamycin DDI [87].

Rifaximin is a non-absorbable (oral bioavailability <1%) rifamycin. It displays a small risk of DDI. According to SPC it is a substrate and a mild inducer of CYP3A. [88] In patients with hepatic insufficiency a DDI with narrow therapeutic index drugs metabolised by CYP3A4 cannot be ruled out due to higher plasmatic concentrations of rifaximin. DDI involving drug transporters caused by rifaximin seems to be unlikely.

1. Anticoagulant and antiplatelet agents. (major)

Many anticoagulant and antiplatelet agents are substrates of CYP enzymes and have narrow therapeutic indices, leading to risk of thrombosis when administered with rifamycin, or bleeding when rifamycin is stopped. A recent review of 29 studies concluded that rifampin in combination with warfarin reduced the AUC of the latter by 15-74% [89]. Two to five-fold increases in warfarin dose are needed to maintain efficacy. Acenocoumarol is similarly affected. The reduction in anticoagulant effects is expected within a week of starting rifampin, and may persist for about 2 to 5 weeks after rifampin has been withdrawn. Rifabutin and rifapentine will likely affect vitamin K antagonists in a similar fashion, but to a lesser extent. This interaction is difficult to manage. It is recommended to avoid the combination or closely monitor INR and ensure a good adherence.

Direct anticoagulants are substrates of CYP3A4 and/or P-gp. A reduction of 20-67% in its exposure (AUC) was seen with rifampin. Such combinations should be avoided or used with great caution and surveillance.[90] Rifabutin and rifapentine will likely affect direct anticoagulants in a similar fashion, but to a lesser extent. In contrast to the previous, heparin has low risk of DDI due to its pharmacokinetic characteristics [90].

Referring to antiplatelet agents, aspirin has scarce risk of DDI. Clopidogrel is a prodrug and CYP2C19 (and possibly CYP3A4) enzymes are responsible for the bioactivation to its active metabolite. Strong CYP2C19 inducers like rifampin increase the exposure to the clopidogrel. Therefore, the risk of bleeding may be increased. As a precaution, avoiding this combination when possible is recommended. In a study of 12 healthy volunteers, rifampin (300 mg twice daily for 14 days) coadministered with clopidogrel (600 mg loading dose followed by 75 mg daily for 7 days) increased the clopidogrel active metabolite AUC and maximum serum concentration approximately 4-fold [91]. Prasugrel is also a prodrug but, in contrast to clopidogrel, coadministration of rifampin (600 mg daily) had no significant effect on the pharmacokinetic parameters of the prasugrel active metabolite or its inhibition of platelet aggregation [92].

2. Inmunosuppressants. (major)

As previously described, rifampin is an inducer of a broad spectrum of enzymes and transporters. Decreases in the blood concentrations of immunosuppressants can have serious consequences. Clinical cases of kidney transplant recipients have reported unusually low levels of cyclosporine when they have been treated with rifampin, resulting in acute graft rejection in one of them [93]. PK studies have determined this was due to an induction of CYP3A4, which disappears after discontinuation of rifampin. In addition to this mechanism, it has been reported that P-gp induction may also contribute to the decrease blood levels of the immunomodulator. Some transplant clinical guidelines recommend avoiding whenever possible the simultaneous use of CNI or mTOR inhibitors with rifampin [49]. However, given the strong sterilizing activity of rifampin in tuberculosis, this drug in not entirely contraindicated in solid organ transplant recipients. When rifampin is used, 2 to 5-fold increments in the daily dose of cyclosporine, tacrolimus and mTOR inhibitors are usually necessary to maintain the immunosuppressant in the therapeutic range. Initially, the dose of the immunosuppressive agent should be doubled and then increased accordingly to daily drug level monitoring until a stable dosage is achieved [49,94]. With close monitoring, the rate of rejection does not seem to be superior with rifampin-based regimens [95]. Adequate adherence to treatment is necessary to avoid fluctuations in blood concentrations. Rifabutin is a less potent CYP3A4 inducer and its use instead of rifampin may make easier the coadministration of CNI and mTOR inhibitors; however, the same recommendations for close monitoring made for rifampin still apply to rifabutin.

Mycophenolate mofetil (MMF) and MPA are substrates of glucuronil-transferases (UGT) and drug transporters (OAT1/3, and OATP1B1/1B3). Rifampin (multiple doses) induces UGT and OATP1B1/1B3. It is recommended to utilize an alternate rifamycin if possible [49].

Prednisolone, the active metabolite of prednisone is a substrate of CYP3A4. Rifampin decreased 28% to 66% the AUC of prednisolone [96]. It is recommended to monitor steroid efficacy and to consider dose increase [49].

3. Other antifungals. (major)

Simultaneous use with CYP3A4 inducers may cause a decrease in bioavailability of azole antifungals and, as a result, a loss of effect. The use of ketoconazole, itraconazole, voriconazole or posaconazole concurrently with a strong CYP3A4 inducer (i.e., rifampin) or within 2 weeks is not recommended. If such a combination cannot be avoided, patients should be closely monitored for evidence of decreased clinical response to antifungal therapy.

The interaction between itraconazole and rifamycin has been reported in several studies and clinical cases over time [97]. In 1998, concomitant administration of itraconazole with rifampin was studied in six patients, it was seen that five of them had an undetectable concentration of antifungal in blood and one had an extremely low concentration [98]. In another study of patients with chronic pulmonary aspergillosis, it was noticed that patients taking these two drugs had 98% lower itraconazole concentrations than patients taking only the antifungal drug [99]. In the case of rifabutin, the results are similar. One study found that 28 patients treated with itraconazole and rifabutin had serum levels of the antifungal 81% lower than 65 patients treated with itraconazole alone [100]. Additionally, rifabutin related toxicity may be seen due to increased rifabutin concentrations. There are no studies of rifapentine with itraconazole, but as it is a metabolism inducer like the other two rifamycins, the recommendations would be the same.

Some case reports also describe a decrease in posaconazole concentrations when rifampin was added to therapy with reductions in posaconazole exposure of 60 to 80%, probably due to UGT induction. In a study in healthy subjects rifabutin (300 mg daily for 17 days) decreased posaconazole's AUC by 49%. Conversely, rifabutin's AUC increased by 72%. This combination should be used only is benefits outweigh risks [87].

In another case-report, rifampin 600 mg daily for 30 days decreased voriconazole's Cmax and AUC by 99% [87]. According to the voriconazole SPC, the combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), with careful monitoring of full blood counts and rifabutin adverse reactions [101].

In a pharmacokinetic study of 24 healthy volunteers, rifampin (600mg daily for 35 days) decreased the isavuconazole (400mg day 1, followed by 100mg daily for 13 days) Cmax and AUC 75% and 97%, respectively [102].

The interaction with fluconazole is milder. Case reports have estimated decreases up to 50% in fluconazole AUC with concomitant rifampin [103]. An increase in fluconazole dosage

Table 7 Summary of clinical relevant DDIs with rifamycins

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
DOACs	Major	Increase of DOACs CYP3A4 and/or P-gp elimination.	20-67% AUC of DOACs	[64]
Warfarin and acenocoumarol	Major	Rifampicin induces vitamin K antagonists metabolism by CYP enzimes.	15-74% AUC of warfarin and acenocoumarol	[67,69]
Immuno-suppresants	Major	Rifampicin induces CYP3A4, and P-gp decreasing blood levels of the immunomodulator. Rifampin induces UGT and OATP1B1/1B3 and increases MMF and MPA elimination. Rifampin induces prednisolone CYP3A4 metabolism.	50% AUC of tacrolimus. 47% AUC of cyclosporine 35% AUC of MMF and MPA. 28-66% AUC of prednisolone	[49]
Azole antifungals	Major	Simultaneous use with CYP3A4 inducers may cause a decrease in bioavailability of azole antifungals and, as a result, a loss of effect. The use of ketoconazole, itraconazole, isavuconazole, voriconazole or posaconazole concurrently with a strong CYP3A4 inducer (i.e., rifampin) or within 2 weeks is not recommended.	60-80% AUC of posaconazole. 99% AUC of voriconazole 97% AUC of isavuconazole 50% AUC of fluconazole	[87,101–103]
Hormonal contraceptives	Moderate	Coadministration of estradiol derivatives and rifamycin causes a decrease in the plasma levels of the former due to metabolic induction by rifamycin.	31-42% AUC of etinyl-estradiol	[105]
Midazolam	Moderate	Concomitant use of midazolam with CYP3A4 inducers causes a reduction in the effect of this benzodiazepine due to a decrease in the exposure (AUC).	69% AUC midazolam	[106]
Other drugs that are major substrates of CYP3A4	Moderate-Major	See Table 1.		

AUC: area under the curve; DDI: drug-drug interaction; DOAC: direct oral anticoagulants; MMF: mycophenolate mofetil; MPA: mycophenolate acid; PK: pharmacokinetics.

may be considered. In case of rifabutin use, no dose adjustment is needed but rifabutin adverse reactions should be monitored.

Rifamycin may be used with other antifungals like amphotericin B or echinocandins. The caspofungin SPC recommends using an increased caspofungin dose of 70 mg daily (after 70 mg loading dose) in adults when coadministered with rifampin [104]. 4.4.4. Hormonal contraceptives. (moderate)

Coadministration of estradiol derivatives and rifamycin causes a decrease in the plasma levels of the former due to metabolic induction by rifamycin. Several studies have shown that CYP3A4 inducers can decrease the AUC of estradiol derivatives by 31-42% [105].

The SPC of the estradiol derivatives warns about a loss of efficiency when they are administered concomitantly with CYP3A4 inducers, recommending the use of an extra method of contraception and the continuation of backup contraception during coadministration and for 28 days after discontinuation of the enzyme inducer to ensure the reliability of the contraception [105].

5. Midazolam. (moderate)

Many PK studies have shown that the concomitant use of midazolam with CYP3A4 inducers causes a reduction in the effect of this benzodiazepine due to a decrease in the exposure (AUC). Induction of both hepatic and intestinal CYP3A4 causes a decrease in the bioavailability of this drug, so orally administered midazolam is more affected than parenterally administered forms. A study with concomitant treatment of IV midazolam and rifampin revealed an increase in the clearance of the first drug from 0.44 +/- 0.2 L x kg/h to 0.96 +/- 0.3 L x kg/h causing a reduction in the effect of the drug [106].

Although there is no information on rifapentine, the recommendation would be similar. In the case of rifabutin, a current review proved a relative dose-dependent induction of CYP3A and P-gp, leading to a 69% decrease in the AUC of midazolam [106].

6. Other drugs. (moderate–major, depending on the drug)

It is difficult to describe them all DDI with rifamycins. Other authors deeply reviewed them [87]. Drugs that are major substrates of CYP3A4 and CYP2C19 (Table 1), and drugs with narrow therapeutic index that are substrates of other enzymes also induced by rifamycin antimicrobials, may have their efficacy reduced when these antimicrobials are added to therapy. Due to the large number of DDI with rifamycins it is always recommended to check them.

In the study conducted by Srinivas NR et al., the impact of rifampicin-induced metabolism on oral versus intravenous

Table 8 Summary of clinical relevant DDIs with fusidic acid

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Statins	Major	This interaction could be driven by the potent inhibition of human OATP1B1/OATP1B3 (involved in hepatic uptake of statins) by FA.	AUC of rosuvastatin, pravastatin, or fluvastatin.	[119]
Warfarin and acenocoumarol	Moderate	Fusidic Acid SPC warns that FA may potentiate the effects of oral anticoagulants, possibly increasing the anticoagulant effects and requiring a reduction in the anticoagulant dose.		[147]
HIV protease inhibitors	Moderate	Co-administration of FA by the systemic route and HIV protease inhibitors, such as ritonavir and saquinavir, may cause an increase in plasma concentrations of both drugs due to possible mutual inhibition of metabolism, which may result in hepatotoxicity.	AUC of FA, ritonavir and saquinavir 2, 1.6 and 3-fold.	[121]

AUC: area under the curve; DDI: drug-drug interaction; FA: fusidic acid; PK: pharmacokinetics.

antineoplastic agents was evaluated. Specifically, it was observed that orally administered antineoplastics such as navitoclax, cabozantinib, cediranib, and idelalisib experienced reduced exposure and increased clearance, not only due to CYP3A4 induction but also due to the induction of Pgp and UGT. Although, intravenously administered drugs like cabazitaxel and romidepsin did not exhibit these effects from rifampicin, as they are not subject to intestinal CYP3A4 and UGT induction, indicating that alterations in their pharmacokinetic profiles are due to other phenomena [107].

Clinical relevant DDIs with rifamycins are summarized in table 7.

ISONIAZID

Isoniazid is an antibiotic used mainly for the treatment and prophylaxis of tuberculosis. It is important to know when using this drug that it is a moderate inhibitor (and weak inducer) of CYP2E1, and a weak inhibitor of CYP3A4, so it can have DDI with drugs metabolized by these enzymes. Some of the drugs with which caution should be exercised are carbamazepine and phenytoin. An increase in the carbamazepine plasma concentration can trigger symptoms of toxicity. Phenytoin toxicity may be greater in patients with reduced metabolism of isoniazid (i.e., those with N-acetyltransferase polymorphisms) [108]. Other drugs that can also be increased by concomitant administration of isoniazid are warfarin, valproate, diazepam or clozapine [7].

A case of severe acetaminophen toxicity was reported in a patient receiving isoniazid.[109] It could be explained by the induction of the CYP2E1 caused by isoniazid, which appears to generate toxic metabolites in the liver. Isoniazid can also act as a monoamine oxidase inhibitor; this interaction may affect some antidepressants and some types of food like wine and some types of cheese. Finally, concomitant treatment of this antitubercular drug with levodopa can cause Parkinson's decompensation. A case report described a deterioration of the patient when he started treatment with rifampin and isoniazid, with an increase of 37% in the AUC and 33% in the Cmax of levodopa. The authors suggested as a possible mechanism an inhibition of the enzyme dopa decarboxylase, probably caused by isoniazid [110].

In tuberculosis therapy, rifampin and isoniazid are often combined. The inducing effect of rifampin on CYP overcomes the inhibitory effect of isoniazid. Therefore, the overall effect of combination therapy is a decrease in drug concentrations of CYP substrates [111].

ETHAMBUTOL AND PYRAZINAMIDE

Ethambutol is used in empirical treatment regimens for *Mycobacterium tuberculosis*. There are few documented interactions, the best known is the one with aluminum hydroxide. Ethambutol should be given 4 hours apart from antacids [112]. Fatty meals reduce the Cmax (22%), and AUC of the drug compared to fasting drug administration. Nevertheless, ethambutol can be taken with or without food [86].

Ethambutol and pyrazinamide have some PD DDI that can be found in their respective SPC.

GLYCOPEPTIDES, LIPOPEPTIDES, AND LIPOGLYCOPEPTIDES

Vancomycin is a glycopeptide antibiotic administered intravenously for treatment of patients with suspected or proven invasive gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). There are a small number of reported interactions of vancomycin with other drugs that are mainly PD (nephrotoxicity, ototoxicity, and neuromuscular block) (see SPC). In newborns, vancomycin clearance was reduced by 18% with concomitant ibuprofen use and by 28% with indomethacin by an alteration in the antibiotic disposition [113]. Finally, orally administered vancomycin may bind to anion-exchange resins such as cholestyramine [9].

Daptomycin is a cyclic lipopeptide that is renally excreted and is not hepatically metabolized, so DDI are unlike because daptomycin neither induces nor inhibits CYP isoforms [114].

Oritavancin is a weak inhibitor of CYP2C9 and CYP2C19 and a weak inducer of CYP3A4 and CYP2D6. Caution should be used during co-administration of oritavancin with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes (i.e., warfarin), as co-administration may increase (i.e., for CYP2C9 substrates) or decrease (i.e., for CYP2D6 substrates) its concentrations. In a study conducted in healthy volunteers, following a single dose of warfarin 25 mg given alone, or administered at the start, 24 or 72 hours after a single 1,200mg dose of oritavancin, the results showed no effect of oritavancin [115].

The DDI potential of dalbavancin is expected to be low. Dalbavancin is not metabolized by CYP enzymes, and it is neither an inhibitor nor an inducer of CYP enzymes. It is not known if dalbavancin is a substrate or inhibitor for hepatic uptake and efflux transporters [116].

AMINOGLYCOSIDES

Aminoglycosides lack important PK DDI but are associated with some clinically relevant PD DDI such as nephrotoxicity, ototoxicity, and neuromuscular blockade which can be consulted in the SPC [117].

CLINDAMYCIN

Clindamycin is a lincosamide antibiotic used for the treatment of anaerobic, streptococcal, and staphylococcal infections. Its major disadvantage is the substantial risk of Clostridium difficile antibiotic-associated diarrhea. Clindamycin is mainly eliminated by the liver and only 5% to 10% is excreted unchanged in the urine. It is a CYP3A4 substrate, this means that inducers of this isoenzyme may decrease the antibiotic concentration, and inhibitors may increase it [118].

FUSIDIC ACID

1. Statins. (major)

Fusidic acid (FA) is a bacteriostatic antibiotic for which *Staphylococcus*, including strains resistant to penicillin, methicillin, or other antibiotics, are especially sensitive. Therefore, it is of interest in the treatment of methicillin-resistant *S. aureus* infections. Cases of rhabdomyolysis, sometimes fatal, have been reported after prescription of FA and a statin. Therefore, this association is contraindicated. Statin therapy should be discontinued for the duration of systemic FA therapy and can be reinstituted seven days after its last dose. Bataillard et al. describe 75 cases of muscle damage related to this DDI reported in the French national pharmacovigilance database (43 cases) and from a literature review (32 cases). The most reported statins were atorvastatin (60%), simvastatin (22.7%), and rosuvastatin (8.0%). Muscle disorders appeared on average 30 days after initiation of FA. Symptoms were muscle weakness (82%), dark urine (71%), and myalgia (61%). Mean creatine kinase level at diagnosis was 43,890 UI/mL, and acute renal injury occurred in more than half of the cases. Outcome was fatal in 22% of cases and 28% kept sequelae at the end of the follow-up (54 days) [119]. This interaction could be driven by the potent inhibition of human OATP1B1/OATP1B3 (involved in hepatic uptake of statins) by FA [120]. This may explain the occurrence of this interaction with statins which are not metabolized by CYP 3A4, such as rosuvastatin, pravastatin, or fluvastatin [119].

2. Warfarin/acenocoumarol. (moderate)

Although specific published data on this interaction are not available, the FA SPC warns that FA may potentiate the effects of oral anticoagulants, possibly increasing the anticoagulant effects and requiring a reduction in the anticoagulant dose.

3. HIV protease inhibitors. (moderate)

Co-administration of FA by the systemic route and HIV protease inhibitors, such as ritonavir and saquinavir, may cause an increase in plasma concentrations of both drugs due to possible mutual inhibition of metabolism, which may result in hepatotoxicity. A case report describes a 32-year-old man who was HIV-positive and being treated with ritonavir, saquinavir, and stavudine who presented with jaundice, nausea, fatigue, arthralgias, and vertigo approximately 1 week after starting FA (500 mg three times/day). The patient's FA was stopped. Serum concentrations of FA, ritonavir and saquinavir were 2, 1.6 and 3-fold higher greater than the upper limit of normal. Symptoms resolved approximately one month after discontinuation of the drugs, and the patient was able to restart antiretroviral treatment [121].

METRONIDAZOLE

1. Warfarin/acenocoumarol. (major)

Metronidazole is an antibiotic derived from nitroimidazoles indicated mainly for anaerobic microorganisms and protozoa. Metronidazole can interact with other drugs due to the ring in its structure that inhibits (weakly) the hepatic metabolism of several pharmacological compounds metabolized by the CYP450 2C9 and/or CYP3A4 isoenzyme [122,123]. Inhibition of these isoenzymes increases the concentration of drugs such as warfarin and other coumarin anticoagulants.

2. Busulfan. (major)

Busulfan toxicity was increased in 14 patients when coadministered with metronidazole as part of myeloablative regimens prior to stem cell transplantation. Trough serum concentrations of busulfan were increased 79% to 87%.

This combination should probably be avoided and, if needed, increased monitoring for busulfan toxicity is recommended [124].

3. Phenytoin. (moderate)

When metronidazole is taken together with phenytoin, the elimination of the antibiotic may be increased because CYP2A6, the isoenzyme responsible for metabolizing metronidazole, is induced, thus requiring a higher dose of metronidazole to achieve the same outcome. Researchers found that concomitant use of phenobarbital and metronidazole reduced the half-life of metronidazole by 33% and increased clearance by 57% [125].

4. Alcoholic beverages. (clinical relevance is uncertain)

Alcoholic beverages should be avoided while taking metronidazole and for at least one day after, due to the patient potentially experiencing disulfiram-like effects. There are several case reports describing a disulfiram-like reaction occurring with the concomitant administration of metronidazole and ethanol. In contrast, metronidazole has not been shown to be an effective component in creating alcohol aversion, and there exists some controversy as to whether this interaction is clinically relevant. This interaction is generally attributed to metronidazole inhibiting aldehyde dehydrogenase, causing a build-up of acetaldehyde in the blood which is ultimately responsible for the subsequent disulfiram-like effects. One study, however, failed to demonstrate an increase in the serum concentration of acetaldehyde after co-administration, so the true mechanism of this interaction is unknown [126].

Clinical relevant DDIs with fusidic acid are summarized in table 8.

OXAZOLIDINONES

Linezolid is an oxazolidinone antibiotic with activity against multidrug-resistant Gram-positive organisms, showing lipophilic features, excellent tissue penetration including the central nervous system (CNS), and weak reversible non-selective monoamine oxidase (MAO) inhibitory effects at therapeutic serum concentrations.

Gatti M et al. deeply reviewed the post-marketing reporting of serotonin syndrome (SS) due to DDIs with linezolid. Their analysis suggests that linezolid is more likely to induce SS when co-administered with citalopram, escitalopram, and methadone [127].

Although linezolid is unlikely to have clinically important interactions at the CYP level, a study in healthy volunteers showed that rifampin 600 mg once daily for 8 days decreased linezolid Cmax and AUC by 21% and 32%, respectively [128]. Other authors have described decreased linezolid trough concentrations during rifampin therapy in patients [129,130]. The clinical significance of this interaction is unknown, and this combination is used in clinical practice. It is strongly recommended that linezolid serum concentrations be monitored in patients with rifampin co-administration or rifampin pretreatment, especially in critically ill patients [129].

Tedizolid inhibits BCRP and increased AUC and Cmax of the BCRP substrate rosuvastatin by approximately 70% and 55%, respectively. Other BCRP substrates such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan also could interact with tedizolid. If possible, its discontinuation should be considered. Tedizolid is a reversible inhibitor of MAO in vitro; however, unlike linezolid, no interaction is anticipated when comparing the IC50 for MAO-A inhibition and the expected plasma exposures in man [131].

TETRACYCLINES

The most used tetracyclines are tetracycline, minocycline, and doxycycline. While tetracycline is majorly excreted by the kidneys, minocycline and doxycycline are metabolized by the liver.

The principal interactions of tetracycline are reflected in the drug absorption and elimination. Concurrent administration of tetracyclines with products containing divalent cations, such aluminum, calcium, magnesium, iron, or zinc, reduced plasma concentrations of tetracyclines from 30% to 90%. Common products containing multivalent cations include antiacids, laxatives, antidiarrheals, multivitamins, sucralfate, molindone, and quinapril tablets. The mechanism of this interaction is based on reactions of chelation, decreased dissolution and binding to antiacid compounds. It is recommended to separate tetracyclines administration of these products by 2 hours to minimize the impact of this interaction [9].

Tetracyclines can increase the plasma concentration of methotrexate; in one case report, the clearance of high-dose methotrexate was reduced by 65% after starting doxycycline [132]. Increases in lithium and ergotamine toxicity have also been described with tetracyclines [133].

The combination therapy with retinoids (isotretinoin, tretinoin, etretinate, and acitretin) is not recommended because of the additive effects on pseudotumor cerebri. The mechanism of this interaction is unclear, but it may be PD, as a result of each agent ability to increase intracranial pressure [134].

TIGECYCLINE

Tigecycline, a semisynthetic derivative of minocycline, is the first agent from the glycylcycline class of antibiotics. Because tigecycline is not extensively metabolized, drugs that inhibit or induce the activity of these CYP isoforms are unlikely to affect the clearance of tigecycline.

The coadministration of tigecycline and a single dose of warfarin in healthy patients resulted in an increase of 88% in R-warfarin AUC and 38% in Cmax, and 29% of S-Warfarin AUC and 38% in Cmax. This increase of warfarin exposure did not alter INR values, because the greatest increase was in the

less active isomer. Even so, it is recommended monitor patients closely if warfarin is co-administered with tigecycline [135].

TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole is a synergistic sulfonamide-containing combination antibiotic, particularly useful by *Pneumocystis jiroveci, Toxoplasma gondii, Stenotrophomonas maltophilia* and community-associated methicillin-resistant *S. aureus.*

Relevant PD DDI are hyperkalemia and bone marrow supression as it is mentioned in the SPC sheet [4].

Sulfamethoxazole is a moderate inhibitor of CYP2C9, the CYP isoenzyme responsible for metabolism of the more potent S-warfarin. This DDI has commonly been associated with the potentiation of anticoagulation induced by warfarin. Sulfonylureas are also affected by the inhibition of these isoenzymes, since glyburide, gliclazide, glimepiride, and glipizide are metabolized by cytochrome P450 2C9. Trimethoprim inhibits 2C8 which is responsible for the metabolism of repaglinide, meglitinide. Several clinical studies report an increase in the plasma concentration of antidiabetics leading to increased pancreatic insulin release and symptomatic hypoglycemia [136–138].

Sulfa drugs may displace methotrexate from plasma protein binding sites resulting in transiently higher levels of unbound methotrexate. Additionally, trimethoprim competes with methotrexate for renal tubular elimination [139].

CONCLUSIONS

To conclude, important DDI with antimicrobial drugs may occur. It is mandatory to review DDIs, especially when antimicrobial therapies with high risk of DDI are used, due to the important consequences that may result from therapy failure in the treatment of an infectious disease, or an increased toxicity. Knowing the mechanism of interactions and their duration once the causative drug has been discontinued can help us in their clinical management.

A limitation of this study is its reliance on a single database PubMed. Although PubMed is a reputable source for medical literature, it may not include certain relevant studies, reviews, or reports that are available in other databases, such as Scopus, Web of Science, or other specialized databases.

FUNDING

None to declare

CONFLICTS OF INTEREST

MT has received honoraria from Janssen, Gilead Sciences, MSD, ViiV Healthcare and Menarini.

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Official journal of the Spanish Society of Chemotherapy

Revisión sistemática

Revista Española de Quimioterapia
doi:10.37201/req/027.2024

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Control precoz del foco de infección en los pacientes atendidos en el servicio de urgencias: una revisión sistemática

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Article history
Received: 25 February 2024; Revision Requested: 5 April 2024; Revision Received: 5 April 2024; Accepted: 17 April 2024; Published: 14 May 2024

RESUMEN

Introducción y objetivo. El término control de fuente (o del foco) abarca todas aquellas medidas físicas que pueden usarse para reducir el inóculo y modificar aquellos factores en el medio infeccioso que promueven el crecimiento microbiano o las defensas antimicrobianas extrañas del huésped. El objetivo principal de esta revisión sistemática (RS) es conocer y comparar si la detección y el control precoz del foco (en menos de 6 horas) en pacientes adultos atendidos en los SUH por infección grave o sepsis, en comparación con el no control del foco o el control del foco diferido (más de 12 horas) es más eficaz y seguro (mejora la evolución clínica, mortalidad, complicaciones, estancia hospitalaria o necesidad de ingreso en UCI).

Método. Se realiza una revisión sistemática siguiendo la normativa PRISMA en las bases de datos de PubMed, Web of Sciencie, EMBASE, Lilacs, Cochrane, Epistemonikos, Tripdatabase y ClinicalTrials.gov desde enero de 2000 hasta 31 de diciembre de 2023 sin restricción de idiomas y utilizando una combinación de términos MESH: "Source Control", "Early" "Infection OR Bacterial Infection OR Sepsis", "Emergencies OR Emergency OR Emergency Department" y "Adults". Se incluyeron estudios de cohortes observacionales. No se realizaron técnicas de metaanálisis, pero los resultados se compararon narrativamente.

Resultados. Se identificaron un total de 1.658 artículos de los cuales se analizaron finalmente 2 que cumplían los criterios de inclusión y fueron calificados de calidad alta. Los estudios incluidos representan un total de 2.404 pacientes con 678 casos en los que se realizó una intervención para controlar el foco (28,20%). En el primer estudio, la mortalidad a los 28 días fue menor en los pacientes que se sometieron a una intervención para el control del foco (12,3% frente a un 22,5%; p<0,001), con HR ajustado de 0,538(IC 95%: 0,389-0,744; p<0,001). En el segundo, se demostró que el tiempo transcurrido desde que el paciente se valora por primera vez y se estabiliza hemodinámicamente, hasta el inicio de la cirugía se asoció con su supervivencia a los 60 días con un OR de 0,31 (IC 95%: 0,19-0,45; p<0,0001). De hecho, por cada hora de retraso se establece un OR ajustado de 0,29 (IC 95%: 0,16-0,47; p<0,0001). De forma que si la intervención se realiza antes de 2 horas a los 60 días el 98% de los pacientes continúan vivos, si se realiza entre la 2-4ª horas se reduce al 78%, si es entre la 4-6ª hora baja al 55%, pero si se realiza con más de 6 horas no habrá supervivientes a los 60 días.

Conclusiones. Esta revisión muestra que el control del foco o fuente realizado tras la evaluación de los pacientes que acuden al SUH disminuye la mortalidad a corto plazo (30-60 días) y que sería recomendable implementar cualquier intervención de control de fuente requerida tan pronto como sea posible, idealmente con carácter precoz (antes de 6 horas).

Palabras clave: Servicios de Urgencias, Infección bacteriana, Sepsis, Control del foco, Precoz

Early source control of infection in patients seen in the emergency department: a systematic review

ABSTRACT

Introduction and objective. The term source (or focus) control encompasses all those physical measures that can be used to reduce the inoculum and modify those factors in the infectious medium that promote microbial growth or foreign antimicrobial defenses of the host. The main objective of this systematic review (SR) is to know and compare whether early detection and control of the focus (in less than 6 hours) in adult patients treated in the ED for severe infection or sepsis, compared to not controlling the focus or delayed focus control

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(more than 12 hours) is more effective and safer (improves clinical evolution, mortality, complications, hospital stay or need for ICU admission).

Method. A systematic review is carried out following the PRISMA regulations in the databases of PubMed, Web of Science, EMBASE, Lilacs, Cochrane, Epistemonikos, Tripdatabase and ClinicalTrials.gov from January 2000 to December 31, 2023 without language restrictions and using a combination of MESH terms: "Source Control", "Early" "Infection OR Bacterial Infection OR Sepsis", "Emergencies OR Emergency OR Emergency Department" and "Adults". Observational cohort studies were included. No meta-analysis techniques were performed, but results were compared narratively.

Results. A total of 1,658 articles were identified, of which 2 that met the inclusion criteria and were classified as high quality were finally analyzed. The included studies represent a total of 2,404 patients with 678 cases in which an intervention was performed to control the focus (28.20%). In the first study, 28-day mortality was lower in patients who underwent an intervention to control the focus (12.3% vs. 22.5%; *P* <0.001), with an adjusted HR of 0.538 (95% CI: 0.389-0.744; *P*<0.001). In the second, it was demonstrated that the time elapsed from when the patient was evaluated for the first time and was hemodynamically stabilized, until the start of surgery was associated with his survival at 60 days with an OR of 0.31 (95% CI: 0.19-0.45; *P* <0.0001). In fact, for each hour of delay an adjusted OR of 0.29 (95% CI: 0.16-0.47; *P*<0.0001) is established. So if the intervention is performed before 2 hours at 60 days, 98% of the patients are still alive, if it is performed between 2-4 hours it is reduced to 78%, if it is between 4-6 hours it drops to 55%, but if it is done for more than 6 hours there will be no survivors at 60 days.

Conclusions. This review shows that source control carried out after the evaluation of patients attending the ED reduces short-term mortality (30-60 days) and that it would be advisable to implement any required source control intervention as soon as possible, ideally early (within 6 hours).

Keywords: Emergency Department, Bacterial Infection, Sepsis, Source control, Early

INTRODUCCIÓN

La atención de pacientes con sospecha de un proceso infeccioso en los servicios de urgencias hospitalarios (SUH) se ha incrementado significativamente en las últimas décadas hasta suponer, al menos, el 15%-35% de todas las atenciones diarias en estas áreas asistenciales en España y en Latinoamérica [1-3]. Asimismo, la gravedad de su presentación clínica y la mortalidad tanto intrahospitalaria como a corto plazo (30 días), también han aumentado en los últimos años, sobre todo en los pacientes que cumplen criterios de sepsis, presentan comorbilidades relevantes, inmunodeprimidos, ancianos, con bacteriemia significativa confirmada desde el SUH y aquellos con un foco o colección infecciosa susceptible de ser drenado (abscesos, fluidos o focos localizados), desbridado (tejido necrótico) o eliminado (dispositivos potencialmente infectados) [1,2,4-7].

La administración precoz y adecuada del tratamiento antibiótico y la toma inmediata de otras decisiones diagnóstico-terapéuticas (solicitar pruebas complementarias, obtener hemocultivos y otras muestras microbiológicas, intensidad del soporte hemodinámico, necesidad de ingreso, etc.), así como específicamente el drenaje de un absceso o foco local de infección, el desbridamiento del tejido necrótico infectado, la eliminación de un dispositivo potencialmente infectado, o el control definitivo de una fuente de contaminación microbiana en curso, repercuten directamente en la supervivencia de los enfermos con infección bacteriana grave [3,6,7,11].

La sepsis y la infección bacteriana grave son claros ejemplos de enfermedad "tiempo-dependiente". El SUH representa uno de los eslabones clave donde se establece la sospecha y el diagnóstico y se inicia el tratamiento guiado por objetivos ("paquetes de medidas en el momento de reconocimiento"), lo que determinará la evolución y el pronóstico del paciente en función de la rapidez de estas actuaciones [1-3]. Pero, hoy en día, además de las cinco medidas establecidas por la guías intenacionales a realizar lo antes posible en el SUH (medir lactato, obtener hemocultivos, administrar antibióticos de amplio espectro, fluidoterapia y vasopresores de forma precoz)[2,12], debe de realizarse una evaluación exhaustiva para determinar si existe un foco infeccioso concreto susceptible de ser identificado y controlado [1-3].

El término control de fuente (o del foco) abarca todas aquellas medidas físicas que pueden usarse para reducir el inóculo y modificar aquellos factores en el medio infeccioso que promueven el crecimiento microbiano o las defensas antimicrobianas extrañas del huésped [6,11]. El control del foco puede incluir el drenaje de un absceso, el desbridamiento del tejido necrótico infectado, la extracción de un dispositivo potencialmente infectado o el control definitivo de una fuente de contaminación microbiana en curso [6,7]. Los focos de infección fácilmente tratables para el control de la fuente incluyen abscesos intraabdominales, perforación gastrointestinal, intestino isquémico o vólvulo, colangitis, colecistitis, pielonefritis asociada con obstrucción o absceso, infección necrosante de tejidos blandos, otras infecciones del espacio profundo (por ejemplo: empiema o artritis séptica) e infecciones por dispositivos implantados [6,7,13-18].

La identificación y control del foco debería lograrse lo antes posible después de la reanimación inicial [2,3,6,7,12-14,19-21]. En relación al tiempo para realizar el control del foco, no existen datos suficientes para establecer una recomendación concluyente, sugiriéndose el control entre las 6 y 12 horas tras el diagnóstico [2,3,6]. En la actualidad, que no se recomiende un control más precoz (en menos de 3 o 6 horas) puede deberse al número limitado de pacientes incluidos en los estudios y a la heterogeneidad de las intervenciones aplicadas, por lo que se puede deducir que cualquier intervención para el control del foco debe realizarse tan pronto como sea posible, ya que se asocia con una mayor supervivencia de enfermos críticos confirmada en estudios observacionales y aleatorizados [2,3,6,7,17-19,22-27].

En general, se debe buscar la opción menos invasiva que pudiera lograr un control efectivo de la fuente [2,6,13]. Las guías de la *Surviving Sepsis Campaign* de 2021 incluyen, dentro de sus recomendaciones de mejores prácticas, sospechar e identificar rápidamente, así como confirmar o descartar un diagnóstico anatómico específico de infección que requiera control de la fuente de forma inmediata e implementar cualquier intervención de control del foco indicada tan pronto como sea logísticamente posible según el centro [2].

El objetivo principal de esta revisión sistemática (RS) es conocer y comparar si la detección y el control precoz del foco (en menos de 6 horas) en pacientes adultos atendidos en los SUH por infección grave o sepsis, en comparación con el no control del foco o el control del foco diferido (más de 12 horas) es más eficaz y seguro (mejora la evolución clínica, mortalidad, complicaciones, estancia hospitalaria o necesidad de ingreso en UCI).

MÉTODOS

Se realizó una revisión sistemática (RS) con base en lo establecido por la lista declaración *Preferred Reporting Items for Sytematic Reviews and Meta-Analyses* (PRISMA) [28]. El protocolo de la revisión ha sido registrado en PROSPERO (ID-497374).

Pregunta PICO. La pregunta de investigación se formuló siguiendo las recomendaciones del formato PICO (Población/paciente, Intervención, Comparador y Outcomes/desenlaces). Nuestra pregunta fue: "En pacientes adultos atendidos en el SUH con sospecha de presentar infección bacteriana-sepsis (**P**), ¿la detección y el control precoz del foco (menos de 6 horas) (**I**) en comparación con el no control del foco o control del foco diferido (más de 12 horas) (**C**) es más seguro y eficaz, de forma que puede mejorar la evolución clínica (sin progresar a shock séptico), mortalidad, complicaciones, estancia hospitalaria, necesidad de ingreso en Medicina Intensiva (**O**)?

Estrategia de búsqueda y criterios de selección. Se realizó una búsqueda bibliográfica en las bases de datos de PubMed, Web of Sciencie, EMBASE, Lilacs, Cochrane, Epistemonikos, Tripdatabase y ClinicalTrials.gov dirigida a localizar artículos que evaluasen y comparasen la eficacia y seguridad de realizar un control del foco infeccioso precoz (entendido como en menos de 6 horas) en comparación con no hacerlo o hacerlo de forma diferida en pacientes adultos atendidos en los SUH.

La estrategia de búsqueda inicial combinó los términos MeSH (*Source Control*) AND (*Infection OR Bacterial Infection OR Sepsis*) de forma inicial en todas las bases de datos sin restricciones de idioma desde 1 de enero de 2000 hasta el 31 de diciembre de 2023. En un segundo paso, se incluyeron los términos (*Emergencies OR Emergency OR Emergency Department*) y, tercero los términos (*Adults*) AND (*Early*). Siendo las estrategias de búsquedas secundarias:*(Emergency OR Emergencies OR Emergency department)* AND *(Source Control)* AND *(Early)* AND (*Infection OR Bacterial Infection OR Sepsis*) y *(Emergency OR Emergencies OR Emergency Department)* AND *(Source Control)* AND (*Infection OR Bacterial Infection OR Sepsis*) AND *(Early)* AND *(adults).*

Finalmente, en todas las secuencias de búsqueda se priorizó la inclusión de RS, RS-metaanálisis, estudios clínicos aleatorizados (ECA) y estudios de cohortes.

Criterios de inclusión y exclusión.

Criterios de Inclusión:

- Pacientes adultos (mayores de 14 años) atendidos en el SUH con la sospecha o confirmación de un proceso infeccioso (con o sin criterios de sepsis) originado en la comunidad. - La valoración clínica, la extracción de las muestras para la analítica, así como de los hemocultivos y otros estudios complementarios y microbiológicos se debe haber hecho en la primera atención del paciente en el ámbito del SUH.
- La búsqueda e identificación del foco, así como indicación de actuación precoz sobre el mismo o su resolución debe ser hecha en el SUH.
- Los estudios proporcionaban una descripción de los grupos de pacientes con y sin intervención sobre el foco, así como de las variables demográficas, epidemiológicas, clínicas, etc.

Criterios de exclusión:

- Pacientes en edad pediátrica (≤ 14 años) o pacientes mixtos (pediátricos y adultos).
- Pacientes atendidos o valorados en otros servicios y entornos (Medicina Intensiva-Críticos, postquirúrgicos, hospitalización, Atención Primaria) o en un entorno distinto al SUH o en entornos mixtos (SUH más otros servicios).
- Posible origen nosocomial del proceso infeccioso.
- Artículos con baja potencia o muestra considerada limitada (escaso número de episodios de infección bacteriana con resolución del foco).
- Estudios de casos y controles, revisiones narrativas, informes de casos, editoriales, comentarios o puntos de vista, cartas al director, resúmenes de reuniones o congresos, presentaciones de carteles/posters, etc.

Extracción de datos y análisis de la calidad. La selección de los artículos se determinó utilizando las fases del método PRISMA [28]: 1.- Identificación, 2.- Cribado, 3.- Elegibilidad (idoneidad) y, 4.- Inclusión definitiva de artículos en la revisión.

De cada estudio incluido se buscó y se extrajo la siguiente información: primer autor; año publicación; país; tamaño de la muestra; tipo y características de diseño del estudio; edad media (o mediana) en años y sexo (% de hombres/mujeres); tipo paciente/proceso/foco o fuente de infección; técnica o método de resolución del foco empleados; tiempo de inicio de las intervenciones para el control; desenlaces analizados, resultados obtenidos (fundamentalmente supervivencia a corto y medio plazo), otras observaciones y conclusiones aportadas por los autores.

Todos estos datos se compararon por tablas (al no realizarse técnicas de síntesis en este artículo).

En el caso de ausencia de ciertos datos relevantes analizados en alguno de los estudios, se intentó contactar con los autores principales para facilitar los datos no publicados o no accesibles. En estos casos, si se recibió respuesta y el dato, se incluyeron. Pero, si no se consiguieron por no existir o no haber respuesta, se excluyó dicho estudio del análisis concreto para el que no se hubiera recuperado la información.

En la fase de elegibilidad cuatro revisores (RLA, MST, VGB y AJJ) realizaron la lectura completa del texto de los artículos y los evaluaron de forma independiente y, posteriormente, extrajeron los datos. En caso de desacuerdo, se discutió con un quinto revisor (DEG) y se llegó a un consenso unánime.

Para valorar la calidad del método empleado y el riesgo de sesgos de los posibles artículos finalmente incluidos se eligieron distintas herramientas según el tipo de artículo incluido. Para estudios de cohortes incluidos en esta RS se utilizó la *Newcastle-Ottawa Scale* (NOS) [29] (valorada individualmente por dos revisores y consensuando las decisiones). Los criterios para la evaluación cualitativa comprendieron tres *ítems* principales: selección de muestra, comparabilidad y exposición. Cada uno de estos *ítems* tenía preguntas con opciones y podría recibir 1 o 2 puntos (estrellas/*) si se cumplían los criterios. Los estudios con puntuaciones totales de 1-3, 4-6 y 7-9 se definieron como de baja calidad metodológica (alto riesgo de sesgos), media y alta calidad (bajo riesgo de sesgos), respectivamente [29].

En el caso de incluir alguna de las RS y metanálisis analizadas en la fase de elegibilidasd se utilizaría la herramienta AMSTAR 2 *(A MeaSurement Tool to Assess Systematic Reviews*) [30] para la evaluación del riesgo de sesgos y la calidad.

No se realizó transformación de los datos ni se abordó el sesgo de publicación.

Finalmente, no se realizaron técnicas de metaanálisis, pero los resultados se compararon narrativamente y se estimaron las medias de los desenlaces críticos.

RESULTADOS

Selección de estudios. El diagrama de flujo de la búsqueda bibliográfica y selección definitiva de los artículos a incluir se muestra en la Figura 1, de acuerdo a las fases del método PRISMA [28]: 1.-Identificación, 2.-Cribado, 3.-Elegibilidad (idoneidad) y, 4.-Inclusión definitiva de artículos en la revisión.

Se identificaron inicialmente 1.658 artículos en las bases de datos seleccionadas. Una vez eliminados los duplicados y tras leer título y resumen, se decidió declarar elegibles a 35 artículos de los que, tras leer el texto completamente, finalmente se incluyeron por unanimidad dos estudios de cohortes no aleatorizados en esta RS [14,22]. Mientras que ocho se descartaron por el tipo de estudio (revisiones narrativas, documentos de consenso o de expertos, etc.) [33-40], uno por incluir niños[41], cuatro por desarrollarse en entornos distintos al SUH (prehospitalario o medicina intensiva)[42-45] y los otros veinte porque no respondían directamente a la pregunta PICO de esta revisión[46-65].

Características de los estudios incluidos. En la tabla 1 se muestran las características de los 2 artículos de cohortes incluidos en esta revisión, finalmente en un idioma (inglés) [14,22] que fueron publicados en el 2014 [14] y en el 2019 [22].

Ambos estudios se desarrollaron en países asiáticos [14,22], uno en Japón [14] y el otro en Corea del Sur [22].

En total se han incluido 2404 pacientes con 678 casos en los que se realizó una intervención para controlar el foco o fuente de infección (23,3% de los casos en el estudio de Azuhata et al [14] y en el 100% de casos en el de Kim et al [22]). Las poblaciones de ambos estudios fueron heterogéneas ya que presentaron un porcentaje de procesos infecciosos y técnicas empleadas para la resolución del foco muy distintas. Así, en el caso del trabajo de Azuhata et al [14] se realizó en todos los casos una intervención quirúrgica tras la estabilización hemodinámica del paciente donde en el 100% de los casos se trataba de una perforación gastrointestinal (estómago, duodeno, intestino delgado, colon o recto). Mientras que en el estudio de Kim et al [22], los focos fueron tracto respiratorio (24,9%) como el sitio de infección más común, seguido del tracto urinario (18,8%) y el tracto gastrointestinal (13,0%). En este estudio, los tipos de control de la fuente consistieron en drenaje percutáneo (57,4%), cirugía de emergencia (19,7%), intervención endoscópica (14,9%), extracción del dispositivo infectado (6,1%) y otros (1,9%).

Asimismo, ambos fueron prospectivos, uno multicéntrico (11 SUH) [22] y el otro unicéntrico [14], todos los pacientes eran adultos con una edad media desde 66 (DE 14) años [14] hasta mediana de 70 (60-78) años [22] y la proporción de hombres fue muy similar (57 frente a 58%) [14,22].

Los dos estudios se elaboraron en pacientes con fiebre y/o sospecha de infección bacteriana con criterios de sepsis y shock séptico según la segunda conferencia internacional (Sepsis 2) [31] el de Azuhata et al [14] y según la tercera conferencia (Sepsis-3) [32] en el de Kim et al [22].

En la tabla 2 se muestra la evaluación de la calidad de los estudios de cohortes incluidos y de sus riesgos de sesgos según la escala NOS. Ambos fueron calificados de calidad alta con 7 puntos (bajo riesgo de sesgos) [14,22].

Desenlaces analizados y resultados obtenidos. En el estudio de Azuhata et al [14] se demostró que el tiempo transcurrido desde que el paciente se valora por primera vez en el SUH y se estabiliza hemodinámicamente, hasta el inicio de la cirugía (horas) se asoció significativamente con su supervivencia a los 60 días con un OR (*Odds Ratio*) de 0,31 (IC 95%: 0,19-0,45; p<0,0001). De hecho, por cada hora de retraso se establece un OR ajustado de 0,29 (IC 95%: 0,16-0,47; p<0,0001). De forma que si la intervención se realiza antes de 2 horas a los 60 días el 98% de los pacientes continúan vivos, si se realiza entre la 2-4ª horas se reduce al 78%, si es entre la 4-6ª hora baja al 55%, pero si se realiza con más de 6 horas no habrá supervivientes a los 60 días.

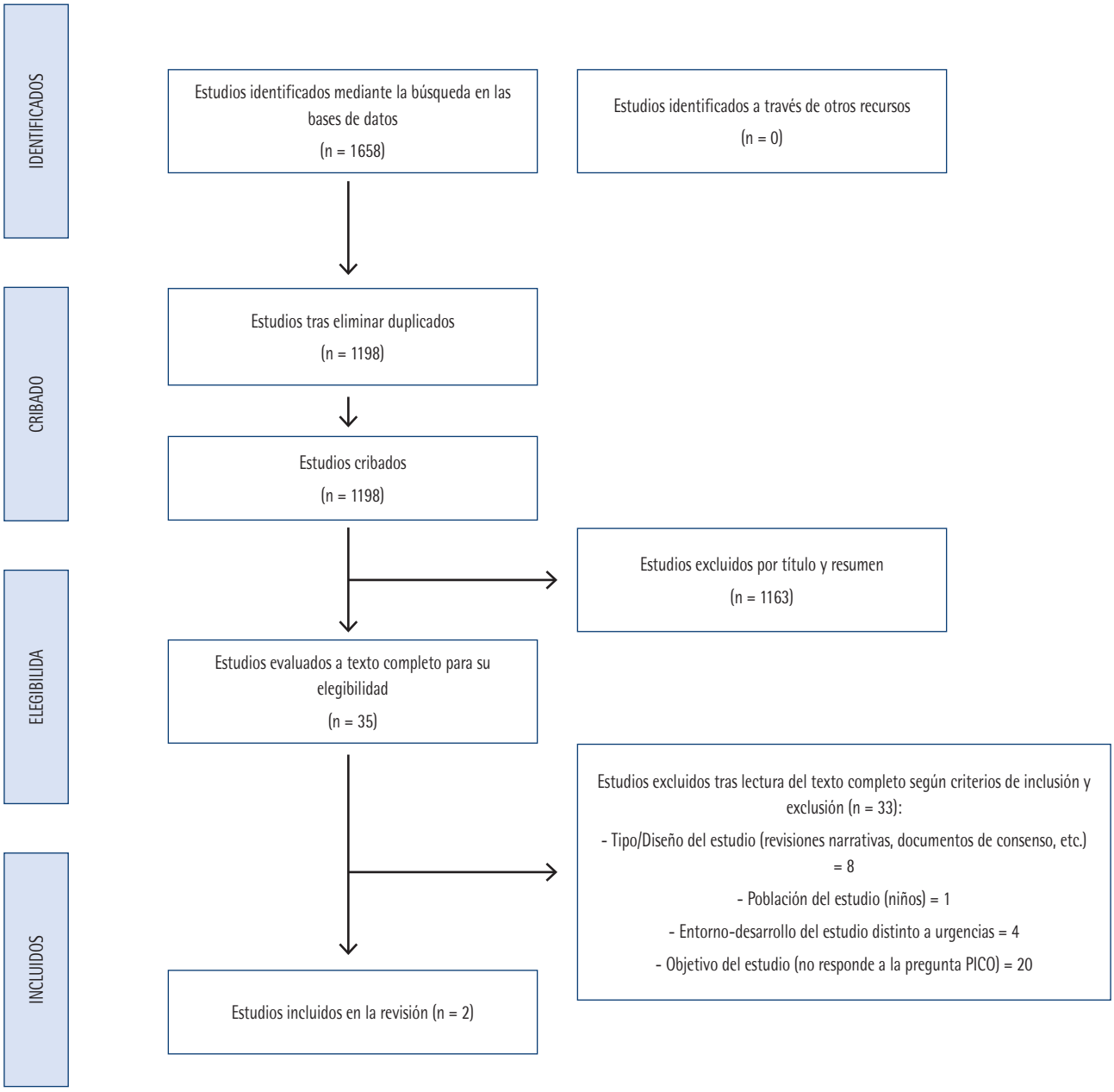

Figura 1 | **Diagrama de flujo de la inclusión de casos**

Por su parte, en el estudio de Kim et al [22] se demostró que la mortalidad a los 28 días fue significativamente menor en los pacientes que se sometieron a una intervención o técnica para el control del foco o fuente indicada en el SUH (12,3% frente a un 22,5%; p<0,001), con HR (*Hazard Ratio*) ajustado de 0,538 (IC 95%: 0,389-0,744; p<0,001). Pero, contrariamente, no se confirmaron diferencias significativas en la mortalidad a los 28 días en relación entre el tiempo de control del foco (precoz en < 6 horas, entre 6-12 horas y mayor a 12 horas). Así, en el análisis multivariable, el control de fuente realizado después de 6 horas y de 12 horas obtuvo una HR ajustada de 1,309 (IC 95%: 0,612–2,797; p=0,488 y HR ajustado de 1,344 (IC 95%: 0,612–2,951; p=0,462), respectivamente. En el subgrupo de pacientes que se sometieron a drenaje con catéter percutáneo (la medida de control más frecuente utilizada en este estudio en el 57,4% de todos los pacientes) tampoco el

Tabla 1 **Características de los estudios incluidos en la revisión**

Autores Año País [Referencia]	n (tamaño de la muestra)	Diseño del estudio	edad (años) Sexo: Hombres (%)	Tipo de: paciente/ proceso/ foco / control	Tiempo medio hasta inicio de cirugía o técnicas para el control del foco	Desenlace/s analizado/s	Resultados obtenidos	Comentarios / Observaciones de los autores
Azuhata et al. Japón 2014 [14]	154	Observacional Prospectivo Unicéntrico	Media 66 (DE: 14) 57%	Pacientes con perforación gastrointestinal con shock séptico asociado*	3,1 (DE 1,5) horas	1.- tiempo desde el diagnóstico hasta el inicio de la cirugía y resultado a los 60 días (superviviente o no) 2.- Determinar la relación con la supervivencia del paciente por cada retraso de 2 horas en el inicio de la cirugía	1.- OR: 0,31 (IC 95%: 0,19-0,45, p<0,0001) Por cada hora de retraso: OR ajustado 0,29 (IC 95%: 0,16-0,47, p<0,0001) Supervivencia a los 60 días: 98 % si inicio en < 2 horas 78 % si inicio entre las 2-4 horas 55 % si inicio entre las 4-6 horas 0 % para > 6 horas hasta el inicio	Para los pacientes con perforación intestinal y shock séptico, junto con la estabilización hemodinámica y la administración de antibioterapia de amplio espectro, el tiempo de inicio de la cirugía es un factor crítico para la supervivencia del paciente y siempre se debe realizar antes de 6 horas
Kim et al. Corea del Sur 2019 [22]	2250	Observacional Prospectivo Multicéntrico (11 SUH)	Mediana 70 (RIC 60-78) 58%	Pacientes con infección sospechada o confirmada y evidencia de hipotensión o hipoperfusión refractaria**	13,3 (RIC 5,9-37) horas	1.- Determinar la relación entre control o no de la fuente y supervivencia a los 28 días. 2.- Determinar relación entre el tiempo hasta control del foco (desde el momento de triaje en el SUH) y la mortalidad a 28 días. 3.- Los resultados secundarios fueron la tasa de ingreso a la UCI, la duración de la estancia en la UCI y el hospital, la aplicación y duración del uso de ventiladores mecánicos y la duración de la estancia en la UCI.	1.- HR: 0,538 (IC 95%: 0,389-0,744; p<0,001) Mortalidad a 28 días del 12,3% en los que sí hubo control de fuente frente a 22,5% en los que no se hizo (p<0,001) 2.- Supervivencia a los 28 días: No hubo diferencias significativas entre los grupos de control del foco < 6 horas, entre 6-12 horas y > 12 horas. 3.- Hubo diferencias en la tasa de VMNI, estancia en UCI	Los pacientes con shock séptico que acudieron al servicio de urgencias y que se sometieron a control de fuente mostraron mejores resultados que aquellos que no lo hicieron. No se pudo demostrar que el desempeño del control rápido de la fuente redujera la mortalidad a los 28 días en pacientes con shock séptico. Se requieren más estudios para determinar el impacto del control rápido de la fuente en la sepsis y el shock séptico.

n: número; DE: desviación estándar de la media; RIC: rango intercuartílico; IC 95%: intervalo de confianza al 95%; SUH: servicio de urgencias hospitalario; UCI: unidad de cuidados intensivos.

***: los criterios de registro para la inscripción fueron: 1) tener 18 años de edad con perforación gastrointestinal (estómago, duodeno, intestino delgado, colon o recto); 2) complicado por shock; 3) reanimación inicial realizada en el servicio de urgencias según protocolo; 4) resección completa de un tracto intestinal necrótico e irrigación/drenaje para peritonitis; y 5) cuidados intensivos postoperatorios en la UCI. La definición de shock estuvo de acuerdo con la de Sepsis-2 [31]: cumplimiento de dos de cuatro criterios para el síndrome de respuesta inflamatoria sistémica (SRIS) y presión arterial sistólica no superior a 90 mm Hg (después de una prueba de líquido cristaloide de 20 a 30 ml por kg de peso corporal durante un período de 30 minutos) o una concentración de lactato en sangre de 4 mmol/L**

****: Los tipos de control de la fuente consistieron en cirugía de emergencia, drenaje percutáneo, intervención endoscópica, extracción del dispositivo infectado y otros. El tracto respiratorio (24,9%) fue el sitio de infección más común, seguido del tracto urinario (18,8%) y el tracto gastrointestinal (13,0%).**

control de la fuente realizado después de 6 horas y 12 horas se asoció con la mortalidad a los 28 días con HR ajustado de 1,085 (IC 95%: 0,479–2,455; p=0,845) y HR de 1,040 (IC 95%: 0,437–2,471; p=0,930, respectivamente.

DISCUSIÓN

Esta revisión sistemática ha evaluado si la detección y el control precoz del foco (en menos de 6 horas) en pacientes adultos atendidos en los SUH por infección grave o sepsis, en comparación con el no control del foco o el control del foco diferido, es más eficaz y seguro. Es decir, si mejora la evolución clínica, disminuye la mortalidad a los 28 y 60 días, aparecen menos complicaciones, disminuye la estancia hospitalaria o la necesidad de ingreso en UCI, entre otros indicadores evolutivos. Todo ello, considerando de forma global todos los pacientes e independientemente del tipo de proceso infeccioso que la hubiera originado y de la intervención realizada. El control del foco puede incluir el drenaje de un absceso, una intervención quirúrgica urgente ante una perforación gastrointestinal, intestino isquémico o vólvulo, colangitis, colecistitis, pielonefritis asociada con obstrucción o absceso renal, el desbridamiento del tejido necrótico infectado de piel y tejidos blandos, drenaje de otras infecciones del espacio profundo (por ejemplo: empiema o artritis séptica) o la extracción de un dispositivo implantado potencialmente infectado o el control definitivo de una fuente de contaminación microbiana en curso [6,7,13-18].

Además, de forma secundaria se ha evaluado el riesgo relativo acumulado de mortalidad por cada unidad de tiempo (una o dos horas) de retraso o demora para realizar la intervención sobre el foco desde que el paciente llega al SUH y es evaluado por primera vez en el triaje.

Los resultados encontrados y conclusiones nos indican la necesidad de adoptar medidas en la práctica clínica en este sentido [1-3,12,13,65].

En el estudio de Kim et al [22] se muestra que en los pacientes que se sometieron a una intervención o técnica para el control del foco o fuente indicada en el SUH, la mortalidad a los 28 días fue significativamente menor (12,3% frente a un 22,5%; p<0,001) con HR (*Hazard Ratio*) ajustado de 0,538 (IC 95%:0,389-0,744; p<0,001). Del mismo modo, estos resultados

Tabla 2 **Calidad de los estudios incluidos con la valoración de la escala Newcastle-Ottawa**

	A.- Selección de la muestras o de las cohortes				B.- Comparabilidad de cohortes sobre la base del diseño o análisis		C.- Desenlace/ resultados			Puntuación Total
Estudio	1	2	3	4	5	6	7	8	9	(riesgo de sesgo)
Azuhata et al. Japón 2014 [14]	*	*	*	-	*	*	*	*	-	7 (bajo)
Kim et al. Corea del Sur 2019 [22]	*	*	*	*	*	-	*	*	-	7 (bajo)

NOS-E: Escala Newcastle-Ottawa para la valoración calidad de los estudios de cohortes incluidos en la revisión
(Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford. asp

refuerzan o corroboran los encontrados y publicados en otras áreas asistenciales, fundamentalmente en los ingresados en las unidades de cuidados intensivos [42-45], pacientes pediátricos [41] o valorados en emergencias extrahospitalarias [43]. Pero, más allá de los resultados de una variable individual, también cuando se valoran los resultados evolutivos dentro de los conseguidos por un paquete de medidas implementadas ("bundle de reconocimiento o inicial") tras la primera valoración del paciente en el SUH [66,67], las distintas intervenciones para el control del foco infeccioso se constituyen como una recomendación clara y necesaria junto con la estabilización hemodinámica (fluidoterapia y vasopresores) y la administración de la antibioterapia adecuada y precoz [1-3,11,33-40,68-70].

En relación con los resultados de mortalidad en función del tiempo hasta que se inicia el control del foco (precoz en menos de 6 horas, entre 6 y 12 horas o más de 12 horas) en el estudio de Kim et al [22] no se encontraron diferencias significativas, ni globalmente en toda la muestra ni en el subgrupo de pacientes que se sometieron a drenaje con catéter percutáneo (la medida de control más utilizada en este estudio en el 57,4% de las ocasiones). Pero, en el estudio de Azuhata et al [14] se demostró que el tiempo transcurrido desde que el paciente se valora por primera vez en el SUH en el triaje y se estabiliza hemodinámicamente hasta el inicio de la cirugía (horas) se asocia significativamente con la supervivencia de los pacientes a los 60 días. Incluso, se concluye que por cada hora de retraso se aumenta la probabilidad de morir del paciente exponencialmente. De forma que si la intervención se realiza antes de 2 horas a los 60 días el 98% de los pacientes continuarán estando vivos, sí se realiza entre la 2ª y 4ª horas la supervivencia se reduce al 78%, si es entre la 4-6ª hora baja al 55% y, finalmente, sí se realiza con más de 6 horas de retraso no habrá supervivientes entre estos enfermos a los 60 días.

Probablemente, estas diferencias entre ambos estudios a la hora de concluir la influencia temporal o no en el pronóstico vital del paciente, se deban a la heterogenidad de los procesos entre ambos estudios y a que en el estudio de Azuhata et al [14] se realiza el control del foco en todos los casos con una intervención quirúrgica tras la estabilización hemodinámica del paciente, mientras que el estudio de Kim et al [22] los focos fueron variados (tracto respiratorio, tracto urinario y tracto gastrointestinal) con realización de diferentes técnicas para el control del foco que sólo se realizó en el 23,3% de los casos (drenaje percutáneo, cirugía de emergencia, intervención endoscópica, extracción del dispositivo infectado u otros).

Aunque se han publicado otras RS y metaanálisis previos sobre la eficacia y necesidad de realizar el control del foco en las seis primeras horas desde su identificación [34-40], ninguna RS-metaanálisis ha evaluado sus resultados en pacientes del SUH desde el año 2000.

En esta RS la evidencia científica que reflejan ambos estudios es limitada por la muestra, sus resultados se muestran coherentes con las recomendaciones internacionales de las Sociedades Científicas implicadas en la atención de estos pacientes [1-3,13,65,70].

En este escenario, las guías internacionales más recientes (*Surviving Sepsis Campaign de 2021*) [2], para adultos con sepsis o shock séptico recomiendan identificar rápidamente el foco o proceso infeccioso e incluir o excluir un diagnóstico anatómico específico de infección que requiera control de fuente emergente, así como implementar cualquier intervención de control del foco requerida tan pronto como sea médica y logísticamente posible (a modo de "Declaración de mejores prácticas") [2,3,12].

De ahí, que esta revisión trata de enfatizar la importancia

de estos resultados para indicar la necesidad de la identificación y resolución precoz del foco, tal y como se recomienda en los servicios de medicina crítica o en pacientes hospitalizados.

Por todo ello, se puede recomendar para los pacientes que acuden al SUH con distintos procesos infecciosos susceptibles de resolución, como pudieran ser abscesos intraabdominales, perforación gastrointestinal, intestino isquémico o vólvulo, colangitis, colecistitis, pielonefritis asociada con obstrucción o absceso, infección necrosante de tejidos blandos, otras infecciones del espacio profundo (empiema o artritis séptica) e infecciones por dispositivos implantados [6,7,13-18,68,70], que estos se identifiquen y se inicie la intervención para su control, lo antes posible y siempre antes de 6 horas desde que el paciente haya sido evaluado en el SUH. Dicha recomendación se uniría a las cinco medidas establecidas por la guías internacionales a realizar lo antes posible en el SUH (medir lactato, obtener hemocultivos, administrar antibióticos de amplio espectro, fluidoterapìa y vasopresores de forma precoz) [2,12,13], debe de realizarse una evaluación exhaustiva para determinar si existe un foco infeccioso concreto susceptible de ser identificado y controlado [1-3].

Esta RS tiene distintas limitaciones que debemos señalar. La principal limitación del proceso de elaboración de esta RS ha sido encontrar artículos que cumplieran los criterios de inclusión y, especialmente, que fueran exclusivos de pacientes adultos y solo atendidos en los SUH. De hecho, se encontraron muchos en la fase de cribado y de elegibilidad cuyo objetivo eran valorar la eficacia de la realización del control precoz del foco, pero, desarrollados en otros entornos asistenciales. Por ello, aunque somos conscientes que este hecho representa una limitación del trabajo y que hay que tener en cuenta para la interpretación y consideración de los resultados y las conclusiones en cada paciente y proceso, desgraciadamente no hay datos suficientes para poder hacer un análisis específico según el proceso/foco infeccioso de origen. Aunque, desde un punto de vista positivo, en el estudio de Kim et al [22] los focos fueron diversos (respiratorio 24,9%, urinario 18,8% y gastrointestinal-abdominal en el 13%) y, además, representan a los tres procesos/focos más frecuentes que originan situaciones de sepsis y shock séptico en los SUH. Por ello, aunque no se puede hacer una análisis detallado y comparativo (metaanálisis) de cada proceso, si podemos interpretar que el control del foco (por los datos de esta RS y los artículos de otros entornos como hospitalización médica y quirúrgica o medicina intensiva) [1-3,13,65,70] se pueden trasladar e implementar de forma general para los distintos procesos/focos y pacientes que acuden a los SUH.

Otra limitación a tener en cuenta de esta revisión es que el sesgo de publicación no ha sido contemplado.

Por otro lado, no se encontraron problemas ni supusieron dificultades las distintas bases de datos, ni el idioma (inglés).

Por último, los autores quieren resaltar la necesidad e importancia de elaborar estudios desde los SUH con pacientes que acuden a ellos con distintos procesos infecciosos comunitarios (del tracto respiratorio, urinario, abdominal, de piel y partes blandas, etc.) que evalúen la eficacia y seguridad de las intervenciones destinadas a controlar el foco o la fuente, tanto en pacientes que ya cumplen criterios de sepsis-shock séptico a su llegada al SUH, como en aquellos atendidos con una infección grave (con bacteriemia acompañante, comorbilidad importante, neutropenia o inmunodepresión, diabéticos, etc.) [2,3,12]. Se necesitan trabajos de investigación del momento óptimo y el método de control de la fuente en pacientes con infección grave, sepsis y shock séptico que son valorados en los SUH.

Como conclusiones, debemos resaltar que aunque no existe un consenso ni evidencia suficiente en relación al tiempo en el que se debe realizar el abordaje del foco, la evaluación exhaustiva para determinar si existe un foco infeccioso susceptible de ser identificado y el proceder a su control, sin duda debe incorporarse al denominado "paquetes de medidas en el momento de reconocimiento" en los SUH. Esta revisión muestra que el control del foco o fuente realizado tras la evaluación de los pacientes que acuden al SUH disminuye la mortalidad a corto plazo (30-60 días) y que sería recomendable implementar cualquier intervención de control de fuente requerida tan pronto como sea posible, idealmente con carácter precoz (antes de 6 horas).

CONFLICTO DE INTERESES

Todos los autores declaran no tener conflictos de interés en relación con este artículo. Ningún autor ha recibido compensación económica ni de ningún tipo por participar en este trabajo.

- AJJ ha participado en reuniones científicas organizadas por Bayer, Sanofi, Boehringer, Esteve, GSK, Lilly, MSD, Pfizer, Tedec Meiji, Roche Diagnostics, Thermo Fisher Scientific, B.R.A.H.M.S. AG, ViroGates y Biomerieux.
- RLA; VGB, MST y DEG declaran la no existencia de conflictos de intereses.

FINANCIACIÓN

Este manuscrito no ha recibido ninguna financiación por parte de ningún organismo ni público ni privado.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/012.2024

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Dalbavancin as consolidation therapy for infective endocarditis in patients with comorbidity. A real world experience

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Article history
Received: 30 January 2024; Revision Requested: 15 April 2024; Revision Received: 10 May 2024; Accepted: 7 June 2024; Published: 17 June 2024

ABSTRACT

Introduction. Infective endocarditis (IE) is a potentially life-threatening infection, the incidence of which has increased in recent decades, particularly among elderly patients with comorbidity. The primary objective of this study was to evaluate the effectiveness of dalbavancin in the consolidation therapy of IE in patients with comorbidity six months after the end of treatment (EOT).

Material and methods. An observational and retrospective study was conducted on patients with a Charlson Comorbidity Index (CCI) ≥ 3 who were diagnosed with IE and received consolidation therapy with dalbavancin.

Results: Forty-eight patients were included, 58.3% were male, mean age of 76.2 years (IQR: 66-88), and a mean age adjusted CCI of 6.5 (IQR: 5-7.5). Definite IE was diagnosed in 77% of cases. The most frequently isolated microorganisms were *Staphylococcus aureus* (45.8%) followed by *Enterococcus* spp. (31.3%). Complications of IE were observed in 67.7% of cases, and cardiac surgery was performed in 27% of patients. The primary reason for using dalbavancin was outpatient parenteral antibiotic therapy in 85.4% of cases. The effectiveness at EOT was 93.8%. At six months, six IE-related deaths, four unrelated deaths, and two IE relapses were observed. The effectiveness was 77%. Adverse effects related to DBV were reported in 4.2% of cases, of which 2% were considered serious.

Conclusion. Dalbavancin has proven to be an effective alternative as consolidation antibiotherapy for IE in elderly patients with comorbidity. Moreover, a very favorable safety profile with few associated adverse effects has been observed in this population.

Keywords: dalbavancin, infective endocarditis, comorbidity, infective endocarditis complications.

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Dalbavancina como terapia de consolidación para endocarditis infecciosa en pacientes con comorbilidad. Una experiencia en mundo real

RESUMEN

Introducción. La endocarditis infecciosa (EI) es una infección potencialmente mortal, cuya incidencia ha aumentado en las últimas décadas, especialmente entre los pacientes ancianos con comorbilidad. El objetivo primario de este estudio fue evaluar la eficacia de dalbavancina en la terapia de consolidación de la EI en pacientes con comorbilidad seis meses después del final del tratamiento.

Material y métodos. Se realizó un estudio observacional y retrospectivo en pacientes con un Índice de Comorbilidad de Charlson (ICC) ≥ 3 diagnosticados de EI y que recibieron terapia de consolidación con dalbavancina.

Resultados. Se incluyeron 48 pacientes, 58,3% varones, edad media de 76,2 años (IQR: 66-88) y un ICC ajustado por edad medio de 6,5 (IQR: 5-7,5). Se diagnosticó EI definitiva en el 77% de los casos. Los microorganismos aislados con mayor frecuencia fueron *Staphylococcus aureus* (45,8%) seguido de *Enterococcus* spp. (31,3%). Se observaron complicaciones de la EI en el 67,7% de los casos, y se practicó cirugía cardiaca en el 27% de los pacientes. El motivo principal del uso de DBV fue la terapia antibiótica parenteral ambulatoria en el 85,4% de los casos. La eficacia al final del tratamiento fue del 93,8%. A los seis meses, se observaron seis muertes relacionadas con EI, cuatro muertes no relacionadas y dos recaídas de EI. La eficacia fue del 77%. Se notificaron efectos adversos relacionados con la DBV en el 4,2% de los casos, de los cuales el 2% se consideraron graves.

Conclusiones. Dalbavancina ha demostrado ser una alternativa eficaz como antibioterapia de consolidación para la EI en pacientes ancianos con comorbilidad. Además, en esta población se ha observado un perfil de seguridad muy favorable con escasos efectos adversos asociados.

Palabras clave: dalbavancina, endocarditis infecciosa, comorbilidad, complicaciones de endocarditis infecciosa.

INTRODUCTION

Infective endocarditis (IE) is a potentially life-threatening infection, the incidence of which has increased in recent decades, particularly among elderly patients with comorbidity [1]. Within this demographic, enterococci and *Staphylococcus aureus* are frequently cited as the primary causative agents [2]. The treatment regimen for IE typically entails prolonged administration of intravenous (IV) antibiotics, often necessitating extended hospitalization periods, frequently coupled with surgical intervention to address the source of infection [3,4].

Dalbavancin (DBV) is a lipoglycopeptide derived from teicoplanin with activity against Gram-positive cocci (GPC), including *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus* spp. [5]. In terms of pharmacokinetics, it boasts a prolonged half-life, allowing for sustained therapeutic concentrations in both plasma and tissues, thereby enabling antibiotic coverage for 1 or 2 weeks following a single IV dose of 1000 mg or 1500 mg, respectively [6]. The metabolism of DBV remains largely unknown, with over half of the compound excreted unchanged in both urine and feces. No dose adjustment is required for individuals with mild to moderate renal impairment, any degree of hepatic impairment, or those undergoing renal replacement therapy. However, dose adjustment is necessary in cases of severe renal dysfunction. Currently, DBV holds exclusive approval for the treatment of acute bacterial skin and skin structure infections, supported by findings from pivotal trials DISCOVER 1 and 2 [8]. In the realm of bloodstream infections, weekly administration of DBV has demonstrated superior efficacy compared to parenteral vancomycin in catheter-related infections [9]. However, evidence regarding the efficacy of DBV in GPC-associated IE among elderly patients with comorbidity remains limited [10-13].

The primary objective of this study was to evaluate the effectiveness of DBV in the consolidation therapy of IE in patients with comorbidity six months after the end of treatment (EOT). Secondary objectives were to determine all-cause mortality at six months after EOT and adverse effects (AEs) related to DBV.

MATERIAL AND METHODS

Study design and population. An observational and retrospective study was conducted on patients with comorbidity and GPC-associated IE, who underwent consolidation treatment with DBV. The study took place in a highly complex tertiary center with 1,423 hospital beds and a reference population of 551,703 inhabitants. The recruitment period spanned from January 2018 to September 2023. The inclusion criteria comprised patients with a Charlson Comorbidity Index (CCI) ≥ 3, who had received at least one dose of DBV, and who were clinically afebrile with negative blood cultures prior to DBV administration. Patients were followed up for six months after their last dose of DBV, constituting the follow-up phase. Clinical management and DBV treatment were adjusted according to the hospital's standard clinical practices.

Outcomes and study definitions. IE was defined by applying the modified Duke criteria updated in 2023 [14]. Early-onset IE was considered if it developed within 12 months after valve replacement, while late-onset IE occurred from 12 months after surgery. Consolidation therapy was considered when DBV was administered as sequential treatment for IE rather than as the initial therapeutic line. The effectiveness of DBV was assessed based on IE failure and cure at EOT and at six months post-EOT. Cure of infection was defined as the absence of microbiological failure and/or clinical signs or symptoms of infection. Microbiological failure was defined as breakthrough bloodstream infection during IE treatment or isolation of the same microorganism in blood culture after completing antibiotic therapy. Failure was defined as a composite of variables: persistence of signs or symptoms of infection, microbiological failure, death, or relapse of IE. Relapse of IE was defined as a second episode of IE caused by the same microorganism during the follow-up period. Mortality was categorized as EOT mortality (death from any cause during hospital stay or within the first month after discharge), mortality during follow-up from the second month after discharge, related (caused by IE complications) or unrelated to IE. The safety profile of DBV was evaluated by documenting AEs attributed to DBV and their severity, as assessed by the necessity to discontinue the antibiotic or the need for therapeutic intervention to manage AEs. The CCI was utilized to assess the 10-year life expectancy of the patients [15]. Plasma level monitoring was not conducted during the study. In patients lacking DBV susceptibility testing, vancomycin sensitivity was regarded as a surrogate indicator of DBV susceptibility [16].

Data collection. Data was collected through the electronic clinical records, including age and sex, comorbidities and CCI, duration of hospital stay and admission to the intensive care unit (ICU); type of IE according to the diagnosis, valve involved and location and presence IE complications; type and duration of previous treatment received (since blood culture negative and/or surgery, if postsurgical culture positive) and concomitant antibiotic treatment; microorganism involved, minimum inhibitory concentration (MIC) of vancomycin and DBV (Etest® method) and susceptibility according to the European Committee for Antimicrobial Susceptibility Testing (EUCAST); dose, dosing regimen, number of doses and duration of DBV treatment, adjusted renal dose, reason for DBV administration and reduction of hospitalisation duration (excluding cases with prolonged suppressive antibiotic treatment) compared to conventional theoretical intravenous treatment and total duration of antibiotics received; cardiac surgery and/or other related surgeries and follow-up blood cultures; cure of infection or failure and microbiological failure at EOT and at six months, mortality at EOT, mortality at 6 months related or not to IE, relapse of IE and AEs related to DBV along their severity.

Ethics considerations. The study adhered to the ethical standards outlined in the Helsinki Declaration. It underwent review by the Galician Drug Ethics Committee (CEIm-G) and

Table 1 Demographic, clinical and treatment characteristics of patients with IE treated with DBV (n=48)

Variable	n (%)
Demographic	
Age (years), mean (IQR)	76.2 (66-88)
Age ≥ 80 years	21 (43.8)
Male gender	28 (58.3)
Medical history	
Solid neoplasm	13 (27)
Hematological neoplasm	5 (10.4)
Solid organ transplant	2 (4.2)
Immunosuppressive treatment	4 (8.3)
Obese	9 (18.8)
Chronic renal disease	13 (27)
Chronic hepatic disease	6 (12.5)
Hemodialysis	1 (2)
Diabetes mellitus	19 (39.6)
Congestive heart failure	17 (35.4)
Cerebrovascular disease	7 (14.9)
Previous IE	6 (12.5)
Chronic lung disease	5 (10.4)
Acute coronary syndrome	6 (12.5)
HIV	1 (2)
CCI, mean (IQR)	6.5 (5-7.5)
IE Type	
Type of valve	
Native valve	24 (50)
Prosthetic valve	18 (37.5)
Early	5 (10.4)
Late	13 (27)
Intracardiac device	5 (10.4)
Intracardiac device and valve	1 (2)
Valve affected	
Aortic	24 (50)
Mitral	11 (22.9)
Tricuspid	6 (12.5)
Aortic and mitral	2 (4.2)

Variable	n (%)
Microbiological isolation	
S. aureus	22 (45.8)
MSSA	13 (27)
MRSA	9 (18.8)
Enterococcus spp.	15 (31.3)
E. faecalis	14 (29.2)
E. faecium	1 (2)
Streptococcus spp.	4 (8.3)
Coagulase-negative staphylococci	7 (14.6)
Unknown	1 (2)
IE complications	32 (67.7)
Septic shock	4 (8.3)
Septic embolism	14 (29.2)
Musculoskeletal manifestations[a]	10 (20.8)
Cardiac complication	18 (37.5)
Heart failure	20 (41.7)
Perivalvular abscess	3 (6.25)
Conduction alteration	2 (4.2)
Neurological complication	6 (12.5)
Ischemic Stroke	5 (10.4)
Cerebral haemorrhage	1 (2)
Acute renal failure	10 (20.8)
Rheumatologic manifestations	2 (4.2)
Leukocytoclastic vasculitis.	2 (4.2)
Treatment	
Reason for DBV use	
OPAT	41 (85.4)
Toxicity of previous treatment	5 (10.4)
Venous access related problems	2 (4.2)
Number of doses of DBV received, mean (IQR)	1.7 (1-2)
Duration of DBV treatment (weeks), mean (IQR), median	3.2 (2-4), 2
Reduction in hospitalisation duration (weeks), mean (IQR)	2.3 (2-4)
Dose adjusted to renal function	4 (8.3)
Cardiac surgery	14 (29.2)
Duration of previous antibiotic treatment, mean (IQR)	3.6 (2-4)
Combination treatment with DBV	14 (29.2)
Rifampicin	13 (27)
Cefditoren	1 (2)

IE, infective endocarditis; DBV, dalbavancin; HIV, human immunodeficiency virus; CCI, Charlson comorbidity index; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus* OPAT, outpatient parenteral antibiotic therapy.

[a]Osteomyelitis, spondylodiscitis, pyomyositis with abscesses of musculoskeletal location.

received approval on July 27th, 2022, with registration code 2022/241.

Statistical analysis. A descriptive study was conducted on the collected variables. Qualitative variables were presented as numbers and frequencies, while quantitative variables were summarized using measures of central tendency (mean and median) and measures of dispersion (interquartile range). The comparison of qualitative variables was carried out using the Fisher's exact test. A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using JASP Team (2024), JASP (Version 0.18.3).

Table 2 Effectiveness and safety outcomes of IE patients treated with DBV (n=48).

Outcomes	n (%)
Effectiveness	
EOT	
Mortality	3/48 (6.2)
Cure of infection	45/48 (93.8)
Follow-up phase (six months)	
Mortality	10/48 (20.8)
Related to IE	6/48 (12.5)
Not related to IE	4/48 (8.3)
Microbiological failure	2/48 (4.2)
Relapse	2/48 (4.2)
Cure of infection	37/48 (77)
Security	
Related AEs	2/48 (4.2)
Severe AEs	1/48 (2)

IE, infective endocarditis; DBV, dalbavancin; EOT, end of treatment; AEs, adverse effec

RESULTS

Patient's characteristics and treatment. Forty-eight patients with comorbidity and GPC-associated IE were included in our study, 58.3% were male, mean age was 76.2 years (IQR: 66-88) and mean age-adjusted CCI was 6.5 (IQR:5-7.5). According to diagnosis, definite IE was present in 77% of patients. It was native in 47.9%, prosthetic in 39.6% and intracardiac device in 10.4%. The most frequent microbiological isolates were *S. aureus* (45.8%) followed by *Enterococcus* spp. (31.3%). Demographic, clinical, microbiological and treatment characteristics are shown in Table 1. MIC to DBV was tested in 33.3% of cases (Table 1 - Supplementary material). The mean duration of hospital stay was 39 days (IQR:22.3-50.3) and 20.8% of cases required ICU admission. Control blood cultures were performed after DBV administration in 75% of the cases. Additional patient characteristics are displayed in Table 1 - Supplementary material.

Effectiveness and security. Cure of infection at EOT was 93.8%. Table 2 shows the effectiveness and security of the 48 patients treated with DBV. Three patients experienced fatal outcomes related to IE at EOT (cases 14, 29 and 48). In all of them, cardiac surgery was not recommended due to their age, comorbidity, and functional status. Case 14 was a frail elderly who two weeks after hospital discharge suffered a progressive worsening of his general condition with acute renal failure and fatal outcome. The case 29 suffered clinical deterioration with acute decompensated heart failure and death two weeks after leaving hospital. Case 48 expired due to severe aortic insufficiency with cardiogenic shock two weeks later discharge clearance. During the follow-up period, two relapses and seven deaths were reported, three related to IE complications (cases 11, 38 and 40). The mean time from hospital discharge to death was 67.2 days (54.3-89.6). Case 38 presented a relapse with poor evolution, multi-organ failure and finally death two and a half months after discharge from hospital. Case 11 was an elderly dependent patient who, three months after hospital discharge, was admitted for decompensated heart failure for depletive treatment, without success. Finally, case 40 presented significant anasarca caused by heart failure and acute renal failure with death, two months after release from hospital. Figure 1 presents effectiveness results of DBV according to the presence or absence of IE related complications, the type of IE, and the microorganism involved. The additional data related to effectiveness of DBV are shown in Table 1 - Supplementary material.

Regarding security, AEs related to DBV have been documented in 4.2% of patients (Table 2). A case with impaired renal function after 3 doses and a case of acute thrombopenia with epistaxis in a patient with a history of autoimmune thrombopenia. This was the only event (2%) considered as severe, requiring antibiotic withdrawal and additional treatment (corticosteroids and immunoglobulins). All AEs were reversible upon completion of DBV treatment.

DISCUSSION

In this real-life study, we present a cohort of patients with IE undergoing DBV consolidation therapy, characterized by advanced age and comorbidity. Prolonged hospitalization resulting from intravenous antibiotic treatment poses significant challenges, including difficulties in venous access, catheter-related infections, and IV-associated falls, thereby considerably impacting the patients' functional status [17]. DBV demonstrates favourable pharmacokinetic/pharmacodynamic (PK/PD) characteristics, allowing for extended dosing intervals that facilitate early patient discharge [6]. The primary reason for DBV utilization in our study was OPAT, which demonstrated a reduction in hospitalization duration of approximately 2 weeks per patient. Additionally, this approach yields positive economic implications compared to conventional antibiotic treatment, as previously noted by other authors [13,18]. Other advantages of DBV include reducing adherence issues and pharmacological interactions (DBV does not interfere with cytochrome P450), especially in polymedicated patients with comorbidity [7].

In our study, the effectiveness rate of DBV in the sequential treatment of IE in patients with comorbidity was 93.8% at EOT and 77% at six months. In the elderly population, previous evidence has shown a significant increase in in-hospital mortality rates, ranging from around 18% to 22%, especially among octogenarian patients with comorbidity, reaching close to 40% [1,19]. The observed effectiveness of DBV in the consolidation treatment of IE is satisfactory to date but difficult to establish due to the lack of uniformity in the definition of infection

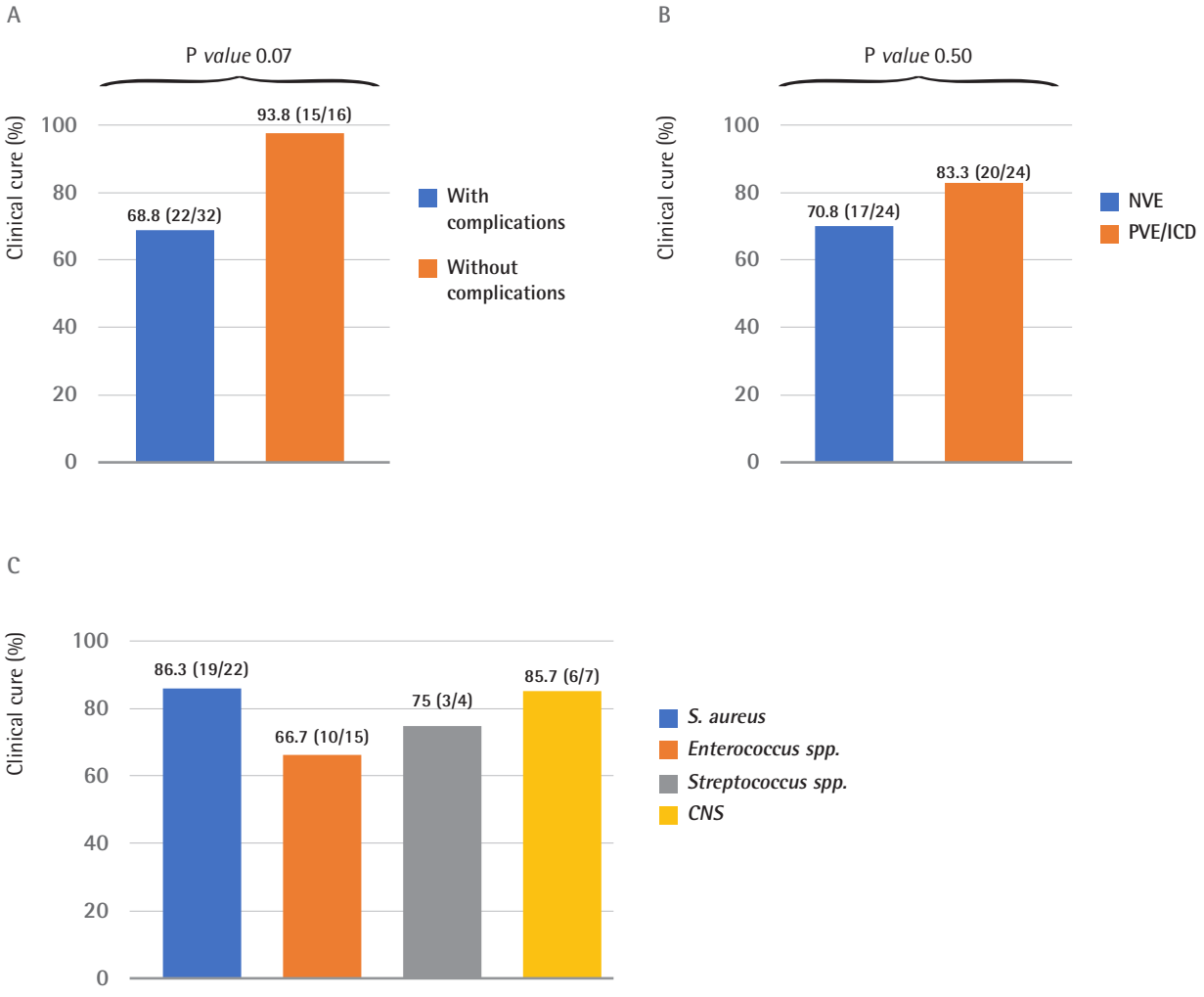

Figure 1 | **Effectiveness of DBV as consolidation at 6 month of IE patients: (A) according to the presence or absence of IE-associated complications, (B) according to the type of IE and (C) according to the microorganism involved.**

DBV, dalbavancin; IE, infective endocarditis; NVE, native valve endocarditis; prosthetic valve endocarditis; IDE, intracardiac devide endocarditis; CNS, coagulase negative *Staphylococcus.*

cure [10-13,20]. In a recent Spanish multicentre study involving 124 IE cases, clinical cure was achieved within 12 months in 95% of patients [21]. Discrepancies in efficacy compared to our study might be attributed to a younger, less comorbid population with a higher proportion undergoing curative cardiac surgery. Recent evidence indicates that surgery can significantly enhance survival within the first year [22]. In our study, only one-third of patients underwent cardiac surgery, thus a lower frequency of surgical interventions and higher mortality rates are characteristic of IE episodes in the elderly compared to the younger population [23]. Furthermore, two-thirds of our population experienced IE-related complications. Cardiac and neurological complications of IE are associated with a poorer prognosis of the infection [24,25]. The presence of complications in our cohort worsened DBV outcomes compared to those without complications.

At the microbiological level, enterococci-associated IE exhibited the poorest outcomes. A recent study comparing DBV to standard of care revealed that at 12 months, *E. faecalis* was responsible for the majority of treatment failures [26]. Nonetheless, other studies involving enterococci demonstrated successful outcomes with DBV in consolidation therapy [20,21]. Furthermore, advanced age and comorbidities that may contraindicate reparative surgery were characteristic factors of enterococcal IE, which could influence the prognosis in our study. Therefore, further research is warranted to elucidate the role of DBV in the treatment of IE caused by *Enterococcus* spp.

In 10% of cases, DBV was employed, withdrawn due to toxicity from previous antibiotics. Despite this, DBV has been shown to have a very favourable safety profile in our cohort of patients with significant comorbidity, with a low incidence of related AEs (4.2%). These findings are in accordance with previously published cohort studies with large numbers of patients [21,27]. In addition, AEs considered as serious were limited (2%), with only one patient requiring DBV withdrawal and additional treatment. In prosthetic cardiovascular infections with indication for implant removal, but without extraction due to contraindication, long-term antibiotic treatment or lifelong antibiotic treatment is recommended [28-30]. A patient who received prolonged treatment with DBV for six months showing adequate tolerance. This fact places DBV as a good alternative to oral therapy for intravascular infections requiring prolonged suppressive treatment, particularly in elderly patients with comorbidity.

Our study has some limitations that should be considered. It is an observational and retrospective study conducted in a single centre, with a heterogeneous population and without a comparator antibiotic treatment group.

In conclusion, DBV offers important advantages due to its pharmacokinetic profile that allows OPAT, shortening hospital stay and reducing complications associated with prolonged conventional intravenous antibiotic therapy. It also reduces adherence problems and drug interactions, especially in polymedicated patients with comorbidity. DBV has proven to be an effective alternative as a consolidation antibiotherapy for GPC-associated IE in elderly patients with comorbidity. Moreover, a very favourable safety profile with few associated AEs has been observed in this population.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/033.2024

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Progression of subclinical cardiovascular disease in patients with HIV

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Article history
Received: 10 April 2024; Accepted: 25 April 2024; Published: 29 April 2024

ABSTRACT

Introduction. Human immunodeficiency virus (HIV) infected patients are at increased risk of cardiovascular disease (CVD). Multidetector computed tomography (MDCT) stratifies cardiovascular risk in asymptomatic patients with subclinical atherosclerosis. The aim of this study was to determine the ability of MCTD and clinical and laboratory parameters to assess subclinical CVD progression in HIV patients.

Material and methods. Prospective longitudinal cohort study of patients with at least 10 years of HIV infection and 5 years of antiretroviral therapy history, low cardiovascular risk and monitored for 6 years (2015–2021). All patients underwent clinical assessment, blood analysis, carotid ultrasound, and gated MDCT in 2015 and 2021.

Results. Sixty-three patients (63.5% male) with a mean age of 49.9 years (standard deviation [SD], 10.5) were included in 2015; 63 of them were followed until 2021. Comparing the results from 2015 with those from 2021, Systematic Coronary Risk Estimation-2 (SCORE2) was 2.9% (SD, 2.1) vs. 4.4% (SD, 3.1); Multi-Ethnic Study of Atherosclerosis score (MESA risk) was 3.4 (SD 5.8) vs. 6.0 (SD 8.6); coronary artery calcification CAC) score >100 was 11.1% vs. 25.4% (P < 0.05); and 11% vs. 27% had carotid plaques (P = 0.03).

Conclusions. After six years of follow-up, an increase in SCORE2, carotid plaques, CAC scoring and MESA risk was observed. MDCT findings, along with other clinical and laboratory parameters, could play an important role as a marker of CVD progression in the evaluation of patients with HIV and low cardiovascular risk.

Keywords: HIV; subclinical cardiovascular disease; multidetector computed tomography; coronary calcium score; intima media thickness.

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Progresión de la enfermedad cardiovascular subclínica en pacientes con VIH

RESUMEN

Introducción. Los pacientes infectados por el virus de la inmunodeficiencia humana (VIH) tienen mayor riesgo de enfermedades cardiovasculares (ECV). La tomografía computarizada multidetector (TCMD) estratifica el riesgo cardiovascular en pacientes asintomáticos con aterosclerosis subclínica. El objetivo del estudio fue determinar la capacidad de la MCTD y los parámetros clínicos y de laboratorio para evaluar la progresión subclínica de la ECV en pacientes con VIH.

Material y métodos. Estudio de cohorte longitudinal prospectivo de pacientes con al menos 10 años de infección por VIH, 5 años de tratamiento, bajo riesgo cardiovascular y seguimiento durante 6 años (2015-2021). Se realizó evaluación clínica, análisis de sangre, ecografía carotídea y TCMD en 2015 y 2021.

Resultados. En 2015 se incluyeron 63 pacientes (63,5% varones) con una edad media de 49,9 años (desviación estándar [DE], 10,5); y fueron seguidos hasta 2021. Comparando los resultados de 2015 y 2021, la Estimación Sistemática de Riesgo Coronario-2 (SCORE2) fue del 2,9% (DE, 2,1) vs. 4,4% (DE, 3,1); La puntuación del Estudio Multiétnico de Aterosclerosis (riesgo MESA) fue de 3,4 (DE 5,8) vs. 6,0 (DE 8,6); el score de calcificación de la arteria coronaria (CAC) >100 fue del 11,1% vs. 25,4% (P < 0,05); y el 11% vs. 27% tenían placas carotídeas (P = 0,03).

Conclusiones. Después de seis años de seguimiento, se ha observado un aumento en SCORE2, placas carotídeas, CAC y MESA. El TCMD, junto con otros parámetros clínicos y de laboratorio, podría desempeñar un papel importante como marcador de progresión de ECV en la evaluación de pacientes con VIH y bajo riesgo cardiovascular.

Palabras clave: VIH; enfermedad cardiovascular subclínica; tomografía computarizada multidetector; puntuación de calcio coronario; grosor íntima media.

INTRODUCTION

Patients infected with human immunodeficiency virus (HIV) are at a higher risk than the general population for developing cardiovascular disease (CVD) [1]. This may be related to various factors, such as genetics, traditional cardiovascular risk factors, antiretroviral treatment (ART), and inflammatory and immunological changes related to HIV itself, regardless of immunovirological control [1]. Therefore, the estimation of an individual's risk of CVD with the greatest possible accuracy is essential for ensuring preventive measures are taken when necessary and should be part of the clinical management of all patients with HIV [1]. In developed countries, the most common cardiovascular manifestation in patients with HIV is ischemic heart disease; therefore, the early diagnosis of CVD is critical to the prevention of acute events, such as acute myocardial infarction or stroke [2].

Cardiovascular manifestations of HIV have changed over the last few decades, following the advent of ART [3]. The overall morbidity and mortality associated with HIV have decreased, although the incidence of coronary heart disease, peripheral artery disease, and heart failure has increased [3]. HIV-related CVD occurs after years of infection, and its prevalence is increasing, due to improved life expectancy in HIV-positive patients treated with ARTs.

A global approach is necessary to prevent atherosclerosis and evaluate risk factors associated with CVD [4]. Cardiovascular risk can be estimated using conventional equations, such as the Framingham score [5] and Systemic Coronary Risk Estimation (SCORE) [6]. In the 2021 European Society of Cardiology preventive guidelines [7], the Systemic Coronary Risk Estimation-2 (SCORE2) algorithm was updated to estimate the 10-year risk of CVD-related death, considering age, sex, lipid levels, smoking status, and blood pressure [8]. In 2022, the National AIDS Plan consensus document on the use of ART in patients with HIV recommended careful cardiovascular risk monitoring in patients who receive integrase inhibitors.

Multidetector computed tomography (MDCT) is useful in the assessment of the extent and severity of atherosclerosis in the vasculature, and in determining coronary artery calcification (CAC) scoring [9]. This score can then be used to classify cardiovascular risk, in addition to conventional risk factors, and may therefore be utilized to make decisions in patients with calculated risks [10]. The Multi-Ethnic Study of Atherosclerosis score (MESA risk) [11] can estimate 10-year CVD risk using traditional risk factors (age, gender, ethnicity, diabetes, smoking status, lipid profile and systolic blood pressure) and CAC. The presence of carotid plaques, measured via ultrasound and CAC, has been found to be a good indicator for further clinical, prognostic, and mechanistic studies of HIV-associated atherosclerosis [12].

The aim of the present study was to determine in patients with at least a 10-year history of HIV and low cardiovascular risk, estimated by classical cardiovascular risk factors, the progression of subclinical coronary atherosclerosis over 6 years, using clinical, blood and imaging tests.

METHODS

Design and inclusion. Prospective longitudinal cohort study of patients with at least 10 years of HIV and 5 years of ART history, monitored by the Infectious Diseases Service of the University Hospital of Santander, Spain, between 2015 and 2021. The inclusion criteria in 2015 were as follows: > 18 years old with HIV; > 10 years since diagnosis; > 5 years of ART; low cardiovascular risk based on the SCORE index; and no previous cardiovascular events. The exclusion criteria were as follows: patients who were not virally suppressed; active or former smokers in the 15 years prior to inclusion; patients who had received < 5 years of ART; the presence of known CVD; patients with systemic inflammatory diseases; and patients who did not sign the informed consent form. Screening was performed on 1,332 patients, with a total of 77 patients being eligible in 2015. During the 6-year follow-up, 14 patients were lost, as follows: 6 did not want to continue the study; 4 were unavailable for testing; and 4 died due to non-cardiovascular causes (Figure 1). During the follow-up period, three patients presented with cardiovascular events (two ischemic strokes and one acute coronary syndrome), and nine developed solid organ tumors.

Data collection assay. Anthropometric and blood analysis data were collected through direct interviews with the patients in 2015 and 2021. In addition to SCORE, SCORE2 was also calculated in both 2015 and 2021, following the last European Society of Cardiology preventive guidelines [7]. Carotid intima-media thickness test (CIMT) was determined via carotid ultrasound, and coronary calcium quantification was determined via gated MDCT, based on the Agatston score, which is the sum of the calcium scores (measured as the Agatston scores of all plaques) in the left main coronary, left anterior descending, left circumflex coronary, right coronary, and posterior descending arteries. Scoring was performed using the current guidelines on CAC screening for cardiac risk assessment [13]. All clinical and analytical data were collected first in 2015 and again in 2021. MDCT was performed in 63 patients in 2015 and in 57 patients in 2021, while carotid ultrasound was performed in 63 patients in 2015 and in 52 patients in 2021. All results were analyzed and compared, and clinical data were collected and reviewed from medical records in the 63 patients included in this study. The following HIV-related parameters were measured: CD4 cell concentration, nadir CD4 cells, and zenith viral load. In addition, erythrocyte sedimentation rate (ESR), ultra-sensitive C-reactive protein (US-CRP), complete blood counts and a lipid profile including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides were recorded.

All 63 patients underwent MDCT on a 64-slice CT scanner to determine CAC in both 2015 and 2021 (Optima; GE Healthcare, USA). Coronary visualization was achieved without contrast using the high-resolution volume mode, and a prospective acquisition technique with heart rate monitoring was used. The amount of calcium in the coronary arteries was

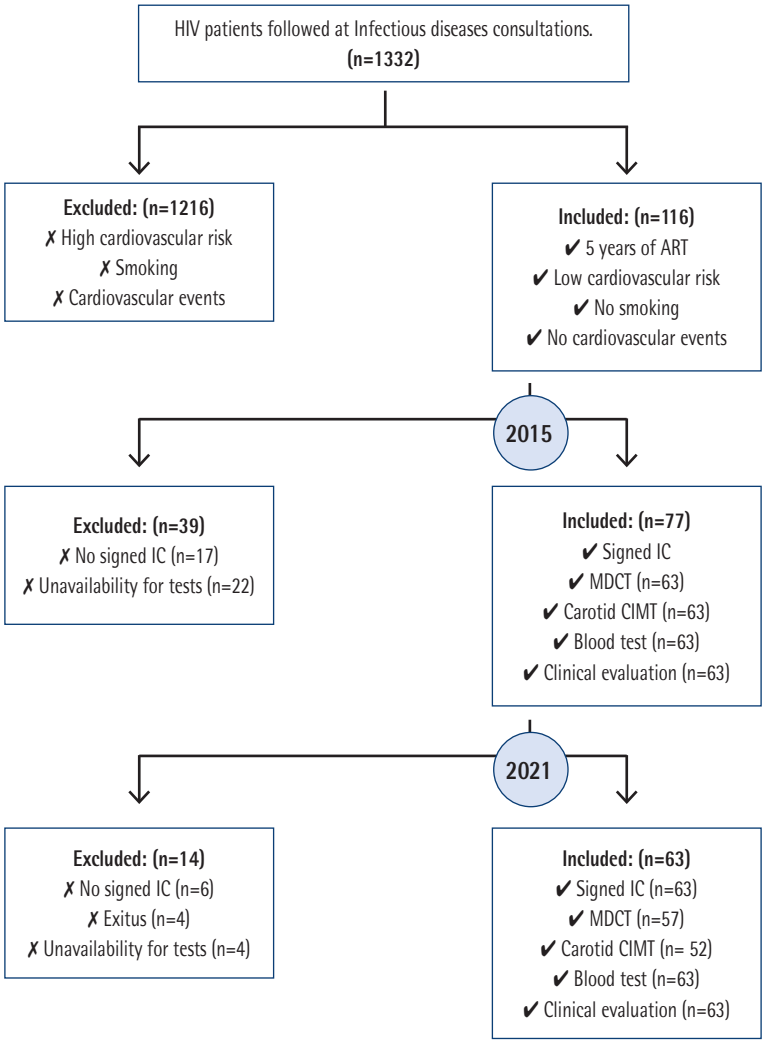

Figure 1 | **Inclusion criteria algorithm.**

Legends: HIV: human immunodeficiency virus. ART: antiretroviral therapy. IC: informed consent. MDCT: multidetector computed tomography. CIMT: carotid intima-media thickness test.

measured using SmartScore® software, and the amount of calcium was expressed using the Agatston score. Patients were categorized into 4 groups, based on their CAC score: 0 (normal); 1–100 (low-to-moderate cardiovascular risk); 101–400 (moderate-to-high cardiovascular risk); and > 400 (high cardiovascular risk) [7]. A CAC score > 100 indicates a high probability of coronary artery disease. According to CAC results, MESA risk [11] was calculated in 2015 and 2021.

CMIT measurements were performed by the same accredited neurologist in 2015 and 2021 using a high-frequency linear transducer (Siemens Acuson X300). All measurements were made using longitudinal and transverse images of the common carotid artery with an 8 MHz probe. For each participant, three measurements were taken on each side, and the result was expressed as the mean CIMT value. Pathological CIMT was defined as ≥ 0.9 mm thickening of the intima-media layer of the arterial wall, and carotid atherosclerosis plaque was defined as a protrusion in the arterial lumen > 1.5 mm, > 50% thickening of the surrounding CIMT, or as the demonstration of a focal protrusion > 0.5 mm in the arterial lumen.

Ethical considerations. The study was performed according to Helsinki Declaration. The protocol was reviewed and approved by the Clinical Research Ethics Committee of Cantabria (Ref: 2015.09, 2021.308) according to local standards. Informed consent was obtained from each patient in 2015 and in 2021.

Table 1 Clinical and analytical characteristics of the study population.

Parameter	Patients 2015 (n = 63) n (%)	Patients 2021 (n = 63) n (%)	P-value*
Age, yr. (mean ± SD)	49.9 ± 10.5	54.4 ± 11.2	-
Sex, male (%)	40 (63.5)	40 (63.5)	-
10-year SCORE	0 (0-1.5)	1 (0-2)	.000
Mean BMI (kg/m2)	26.3 ± 4.2	27.4 ± 4.3	.02
Smoker			.000
Active	3 (4.8)	5 (7.9)	-
Former smoker	24 (38.1)	26 (41.3)	-
Never	36 (57.1)	32 (50.8)	-
Median pack-years	12 (7-22)	12 (7-21)	.09
DM	1 (1.6)	7 (11.1)	.01
HBP	11 (17.5)	27 (42.9)	.001
Statin treatment	8 (12.7)	20 (31.7)	.000
Lipid profile			
HDL cholesterol	51.6 ± 18.8	55.0 ± 25.4	.27
LDL cholesterol	109.1 ± 34.5	120.3 ± 42.8	.033
Total cholesterol	183.4 ± 50.5	190.6 ± 48.8	.36
Triglycerides	152.8 ± 125.0	143.8 ± 109.4	.50
Kidney function			
Creatinine (mg/dL)	0.88 ± 0.2	0.92 ± 0.25	.02
CKD-EPI (ml/min/1.73 m2)	87 ± 8.4	81 ± 12.9	.000
HIV			
Zenith VL	245,135 ± 758,358	245,135 ± 758,358	-
TCD4 (cells/uL) lymphocytes	693.6 ± 373.6	609.5 ± 286.1	.011
TCD4/TCD8	0.9 ± 0.4	1.0 ± 0.5	.017
Months since HIV diagnosis	207.9 ± 81.8	267.9 ± 81.8	.24
ART (months)	167.2 ± 75.3	227.6 ± 75.3	-
Inflammation markers			
ESR	12.8± 10.9	17.5 ± 19	.03
US-CRP	0.13 ± 0.13	1.7 ± 1.6	.000

BMI, body mass index; SD, standard deviation; VL, viral load; HIV, human immunodeficiency virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DM: diabetes mellitus; HBP, high blood pressure; ESR, erythrocyte sedimentation rate; US-CRP, ultra-sensitive C-reactive protein; SCORE, Systemic Coronary Risk Estimation. *Two-tailed chi-square test for qualitative variables and Student's t test for paired two-tailed data for quantitative variables.

Table 2 SCORE (Systemic Coronary Risk Estimation), SCORE2 (Systemic Coronary Risk Estimation-2), MESA risk (Multi-Ethnic Study of Atherosclerosis score), Coronary artery calcium (CAC), and carotid intima-media thickness test (CIMT) results.

Parameter	Patients 2015 (n = 63)	Patients 2021 (n = 63)	P-value*
SCORE mean ± SD	0.9 ± 1.2	1.4 ± 1.7	.000
SCORE2 mean ± SD	2.9 ± 2.1	4.4 ± 3.1	.000
MESA risk mean ± SD	3.4 ± 5.8	6.0 ± 8.6	.000
Agatston mean ± SD	85.4 ± 415	242.5 ± 10,169.5	.04
0 (normal)	45/63 (71.4)	28/57 (49.1)	.000
1-100 (low-to-moderate CVR)	11/63 (17.5)	13/57 (22.8)	.23
> 100	7/63 (11.1)	16/57 (28.1)	.000
101-400 (moderate-to-high CVR)	4/63 (6.3)	12/57 (21.1)	.006
> 400 (high CVR)	3/63 (4.8)	4/57 (7)	.000
CIMT			
CIMT (mm), mean ± SD	0.74 ± 0.15	0.82 ± 0.14	.000
CIMT (mm) > 0.9, n (%)	10/63 (15.8)	14/52 (26.9)	.01
Carotid plaques, n (%)	7/63 (11.1)	15/52 (28.8)	.03

SCORE, Systemic Coronary Risk Estimation; SCORE2, Systemic Coronary Risk Estimation-2. MESA risk: Multi-Ethnic Study of Atherosclerosis score; CAC, coronary artery calcium; CVR, cardiovascular risk; CIMT, carotida intima-media thickness; SD, standard deviation. *Two-tailed chi-square test for qualitative variables and Student's t test for paired two-tailed data for quantitative variables.

Statistical analysis. Quantitative data were presented as mean and standard deviation (SD), or as median with absolute ranges or interquartile ranges (Q1-Q3). Qualitative variables were summarized using absolute and relative frequencies, along with 95% confidence intervals (CI). Each variable was assessed for its parametric or non-parametric distribution using the Kolmogorov-Smirnov test. To detect differences between two quantitative variables, paired Student's t-test was used, while the chi-square test was employed for comparisons between two qualitative variables. Pearson's correlation coefficient (R) with a linear regression model was utilized for correlation analysis between two parametric quantitative variables. Multiple linear regression analysis was performed for certain quantitative variables, both unadjusted and adjusted for age, sex, and cardiovascular risk factors. A two-tailed P value of < 0.05 was considered statistically significant. Statistical analyses were conducted using STATA/IC 16.1.

RESULTS

Demographics and comorbidities. The study population included in 2015 was 77 patients, but only 63 patients were compared between 2015 and 2021 and were included in the analysis as mentioned above (Figure 1).

Table 3 **Correlation between coronary artery calcium (CAC), carotid intima-media thickness test (CIMT), coronary artery calcium score (SCORE), classic cardiovascular risk factors and HIV-related analytical parameters.**

Parameter	CAC correlation in 2021		CIMT correlation in 2021	
	R	P-value	R	P-value
SCORE in 2021	0,13	0,34	0,53	0,0001
SCORE2 in 2021	0.3	0.03	0.55	0.000
MESA risk 2021	0.79	0,000	0.54	0.000
CIMT in 2021	0.26	0,07	-	-
Classical CVR factors in 2021				
HBP	-0,19	0,16	-0,24	0,09
DM	-0,45	0,001	-0,49	0,001
Sex	-0,17	0,21	-0,3	0,03
Age	0,19	0,15	0,45	0,001
Tobacco	0,11	0,43	0,03	0,85
BMI	-0,08	0,6	0,16	0,27
Lipid profile				
LDL cholesterol	-0,21	0,13	0,03	0,85
HDL cholesterol	-0,14	0,31	-0,13	0,37
Total cholesterol	-0,2	0,15	0,01	0,96
Triglycerides	0,04	0,8	0,22	0,12
HIV factors				
CD4 2021	-0,06	0.66	-0,16	0,25
Nadir CD4 at diagnosis < 200	0,15	0,28	0,29	0,04
Zenith VL > 200,000	0,03	0,84	0,17	0,23
Months on ART	0,04	0,76	0,04	0,79
ART (months)				
PIs	-0,05	0,74	0,12	0,42
NRTIs	0,02	0.9	0,06	0,69
NNRTIs	-	0,71	0,3	0,03
INIs	0,05	0,27	0,18	0,21
Inflammation markers				
ESR	0,42	0,002	0,3	0,03
US-CRP	0,29	0,04	0,06	0,68

R, Pearson correlation coefficient; CAC, coronary artery calcium score; SCORE, Systemic Coronary Risk Estimation; CIMT, carotid intima-media thickness; CVR, cardiovascular risk; HBP, high blood pressure; DM, Diabetes mellitus; LDL, low-density lipoprotein; HIV, human immunodeficiency virus; VL, viral load; ART, antiretroviral therapy; PIs, Protease inhibitors; NRTIs, Nucleoside reverse transcriptase inhibitors; NNRTIs, Non-Nucleoside transcriptase inhibitors; INIs, integrase inhibitors; ESR, erythrocyte sedimentation rate; US-CRP, ultra-sensitive C-reactive protein.

The clinical and analytical characteristics are listed in Table 1. The mean ± SD age in 2015 was 49.9 ± 10.5 years, and most patients were men (63.5%). In 2015, 17.5% (n = 11) of the patients had high blood pressure and 12.7% (n = 8) were receiving statin treatments. In 2021, 42.9% (n = 27) had high blood pressure, while 31.7% (n = 20) were receiving statins. LDL went from a mean of 109.1 ± 34.5 mg/dL to 120.3 ± 42.8 mg/dL, and total cholesterol went from 183.4 ± 50.5 mg/dL to 190.6 ± 48.8 mg/dL. The value of ESR increased from 4.7 mm/h (P = 0.03), and US-CRP 1.6 mg/mL (P < 0.01). A decrease in renal function was observed, evidenced by an increase in creatinine of 0.04 mg/dL (P < 0.05).

Table 4 **Correlation between coronary artery calcium (CAC) score and the presence of carotid plaques in 52 patients in 2021.**

CAC in 2021	Carotid plaque in 2021 (n = 52)		
	No, n/N (%)	Yes, n/N (%)	P-value*
0 (normal)	23/24 (95.8)	1/24 (4.2)	.000
1–100 (low-to-moderate CVR)	8/10 (80)	2/10 (20)	.12
101–400 (moderate-to-high CVR)	2/11 (18.2)	9/11 (81.8)	.000
> 400 (high CVR)	1/4 (25)	3/4 (75)	.023

CAC, coronary artery calcium; CVR, cardiovascular risk; CIMT, intima-media thickness. *Two-tailed chi-square test for qualitative variables.

SCORE2 risk, CAC score and MESA risk results. In cardiovascular risk assessment, the mean SCORE in 2015 was 0.9 ± 1.2, compared to 1.4 ± 1.7 ($p < 0.05$) in 2021. Likewise, the SCORE2 in 2015 was 2.9 ± 2.1 compared to 4.4 ± 3.1 ($p < 0.05$) in 2021.

MDCT findings are presented in Table 2. In 2015, 22 patients (34.9%) exhibited coronary plaques, compared to 29 (46%) in 2021 ($P < 0.05$). In 2015, 7 patients (11.1%) had a CAC score > 100, compared to 16 (25.4%) in 2021 ($P < 0.05$). In the group at low cardiovascular risk (SCORE < 1), most patients (14/19; 73.7%) had a normal CAC score (CAC = 0). However, the remaining 5 (26.3%) low-risk patients had findings of low-to-moderate CAC (CAC 1–100) ($P = 0.007$). In the group at high cardiovascular risk (SCORE > 5), all patients (3/3) had a CAC score > 100 ($P = 0.036$). MESA risk in 2015 (including cardiovascular risk factors and CAC) was 3.4 ± 5.8 compared to 6.0 ± 8.6 ($p < 0.05$) in 2021.

The correlation between CAC, SCORE, SCORE2, MESA risk, classic cardiovascular risk factors (high blood pressure, diabetes mellitus, sex, tobacco use), HIV-related factors, and carotid plaques is shown in Table 3. A strong positive correlation of CAC in 2021 with MESA risk was found ($R = 0.79$, $P = 0.000$). Also, a significant moderate positive correlation of CAC in 2021 was found with SCORE2 ($R = 0.3$, $P = 0.03$), and the inflammation markers ESR ($R = 0.42$, $P = 0.002$) and uCRP ($R = 0.29$, $P = 0.04$). A multivariate analysis of CAC, adjusted for parameters of cardiovascular risk (age, sex, high blood pressure, diabetes mellitus, cholesterol, triglycerides, and body mass index) was performed, with an R of the CAC score of 0.19 ($P = 0.04$).

After 6 years of follow-up, 2 episodes of cerebral stroke and 1 episode of acute myocardial infarction occurred. One of the patients had a cerebral stroke in 2015 and died before 2021 due to advanced prostate cancer. This patient, therefore, was excluded from the 2021 study. Another patient suffered a stroke in 2017, with a high SCORE2 of 6 in 2015 and 12 in 2021, a low-to-moderate CAC score of 12 in 2015 with a moderate-to-high CAC score of 245 in 2021; and a high MESA risk in 2015 (4) and 2021 (6). The patient who suffered acute myocardial infarction in 2012, had a high SCORE2 in 2015 and 2021 (9), and a very high CAC (3,212 in 2015 and 7,900 in 2021) and MESA risk (33 in 2015 and 47 in 2021). MDCT was useful in detecting a pulmonary nodule in 4 patients and a renal nodule in 1 patient.

Carotid plaques and Intima-media thickness results. The mean CIMT was 0.74 mm ± 0.15 in 2015, compared to 0.82 mm ± 0.14 in 2021 ($P < 0.05$). There was a significant difference between the presence of CIMT > 0.9 mm and carotid plaques in 2015 and 2021, as shown in Table 2. There were no cases of carotid stenosis greater than 50%.

Table 3 shows the correlation between CIMT, SCORE, SCORE2, MESA risk, classical cardiovascular risk factors (high blood pressure, diabetes mellitus, sex, tobacco use), HIV-related factors, and carotid plaques. A moderate positive correlation of CIMT in 2021 was found with SCORE2 ($R = 0.55$, $P = 0.000$), MESA risk ($R = 0.54$, $P = 0.000$), SCORE ($R = 0.53$, $P = 0.000$), age ($R = 0.45$, $P = 0.001$) and ESR ($R = 0.3$, $P = 0.03$). When categorized by CAC there was a significant increase in carotid plaques in patients with a CAC score > 100 ($P < 0.05$). (Table 4).

DISCUSSION

A higher incidence of atherosclerosis among HIV-infected patients has been demonstrated in previous studies [14-16], and subclinical atherosclerosis can be assessed using the CAC score [17-19]. In the present study, we evaluated the usefulness of MDCT in quantifying the progression of coronary calcium levels and assessing the evolution of cardiovascular risk in a cohort of patients with long-term HIV. The detection of subclinical coronary atherosclerosis through CAC and CIMT metrics allowed us to identify patients with HIV with an underestimated cardiovascular risk based on classic cardiovascular risk factors but a high risk of experiencing fatal cardiovascular events, who will benefit from primary preventive treatment. Each diagnostic test and its relationship with the HIV-related parameters are discussed below.

During the 6 years of follow-up in patients with at least 10 years living with HIV, we observed a significantly increased incidence of classic cardiovascular "classical" factors, such as Diabetes Mellitus and high blood pressure. As well as signif-

icant increase in creatinine, ESR, US-CRP, and a decrease in CD4 T cell levels.

Searching for subclinical atherosclerosis we observed a significantly accelerated progression of subclinical CAC after six years of follow-up, like other studies. Soares et al. [19] observed in their meta-analysis that HIV patients have higher prevalence of noncalcified coronary plaques measured by coronary CT angiography and similar prevalence of CAC measured by MDCT, compared with HIV- negative individuals. The aim of our study was instead to detect the progression of CAC rather than studying its prevalence. Also, we didn't perform coronary CT angiography, so noncalcified plaques were not analyzed. Volpe et al. [20] found comparable findings after a 6-year follow-up of 211 HIV-positive participants, and Guaraldi et al. [21] also found similar findings after 11 months of follow-up in 132 HIV-positive men on ART. In the present study, MESA risk and SCORE2 were also significantly increased in HIV patients, with a strong correlation between MESA risk and CAC, and a moderate correlation between SCORE2 and CAC. Based on these results, it could be suggested that a low SCORE or SCORE2 may underestimate the presence of subclinical cardiovascular disease. These findings are similar to those of Rueda-Gotor et al. [22], who also concluded that SCORE underestimates the cardiovascular risk in rheumatologic patients. Thus, MDCT and MESA risk may be useful for evaluating HIV patients with a low to moderate cardiovascular risk and SCORE2. These patients may benefit from intensity primary preventive treatment of cardiovascular risk factors, such as Diabetes Mellitus and high blood pressure, since a detected higher-than-expected CAC and MESA risk, increase their calculated cardiovascular risk [7, 11]. In addition, it has been suggested that patients who may benefit from the preventive management of cardiovascular risk factors, to repeat CAC scoring at an interval of 5 years for patients with a CAC score of 0, and a 3–5-year interval for patients with a CAC score > 0 [23].

The only patient who experienced a stroke during the follow-up period in the present study had a high SCORE2 (6,12), a moderate-high MESA risk (4, 12) in 2015 and 2021, and low-to-moderate CAC score in 2015, and moderate-to-high CAC score in 2021. In this case, MDCT had a good ability to predict an ischemic episode in an HIV patient with subclinical cardiovascular disease and a moderate risk of cardiovascular events in 2015. This could suggest that both SCORE2, MESA risk and MDCT could detect the evolution of cardiovascular disease, during the 6 years of follow-up.

Regarding the relationship between CD4 cell count and viral load at HIV diagnosis, analyzed in 2015 and 2021, we observed in 2015 that low CD4 cell count, and high zenith viral load were associated with a higher CAC score, despite a low SCORE2 index [24]; however, after 6 years of follow-up, no correlation was found between CAC score and nadir CD4 cells or zenith viral load at HIV diagnosis. The results of previous studies are contradictory while Volpe et al. [20] and Guaraldi et al. [21] did observe a relationship between CAC progression and low CD4 cells and high viral load; Chow et al. [25] did not observe such association between CD4 cells, viral load, and CAC. These differences may be explained by the age of patients, in fact that our patients were older, and had an increased prevalence of classic CV factors and cardiovascular risk. A long-term follow-up of > 10 years might be useful to determine if the correlation between CAC and HIV factors changed.

A few studies have evaluated CIMT in HIV patients [26]. A meta-analysis in 2019 included 17 studies comparing CIMT between patients with HIV and control patients, and the CIMT of those with HIV was 0.27 mm thicker ($P < 0.027$) [26]. Hsue et al. [3] observed an association between HIV and the progression of CIMT and found that patients with HIV had a higher CIMT than HIV-negative patients, with or without detectable CAC. Other studies have described an increase in CIMT progression after ART initiation, with protease inhibitors or nucleoside reverse transcriptase inhibitors (NRTIs) [27,28]. In the present study, 20% of patients with MDCT findings of low risk (CAC score = 0) exhibited carotid plaques, compared to 82% and 75% of patients with moderate and high risk, respectively. These results suggest that the presence of severe carotid ultrasound findings may be considered a reliable predictor of CVD, as concluded by Spence et al. [10], and a reliable way of identifying high-risk cardiovascular patients, according to the most recent European Guidelines on cardiovascular disease prevention in clinical practice [7]. We found a good correlation between CIMT, MESA risk and SCORE2. However, we did not observe a good correlation between CAC and CIMT. Lester et al. [29] reported this discrepancy in 89 healthy patients with low cardiovascular risk and a CAC score = 0, with the presence of 34% of carotid plaques. Naqvi et al. [30] detected 52% of carotid plaques in 136 asymptomatic patients with low risk and CAC score = 0 [30]. An explanation for these findings may be the limitation of MDCT in detecting non-calcified plaques in the early stages of CVD.

Regarding factors associated with HIV, a moderate correlation was found between CIMT and CD4 T-cell nadir levels < 200 cell/mL and months of nevirapine treatment. These data suggest that CIMT may be a more sensitive technique than CAC (coronary artery calcification) for detecting the relationship between HIV-associated factors and the presence of CVD. Therefore, it would be of interest to conduct further studies in the future with a larger sample size, in which this relationship can be analyzed in more detail.

Concerning inflammation markers, a significant increase was detected in ESR and US-CRP. ESR values increased by 4.7 mm/h ($P = 0.03$), and US-CRP levels increased by 1.6 mg/mL ($P < 0.01$). Several clinical studies have associated elevated ESR levels with an increased risk of mortality from coronary artery disease and the progression of atherosclerosis [31-32]. Erikssen et al. [33] assessed ESR in healthy patients aged 40 to 60 years, and the test was repeated after a 7-year follow-up. ESR was correlated with mortality from coronary artery disease, leading to the conclusion that it may serve as a marker for aggressive forms of coronary artery disease. In contrast, our study did not include patients with established or symptomatic cardiovascular disease, but we still observed an increase in ESR in patients with subclinical cardiovascular disease progression. These find-

ings suggest that ESR determination is a valuable and sensitive test for evaluating inflammation associated with atherosclerosis, and it may provide important short-term prognostic information in the case of subclinical cardiovascular disease and long-term or established cardiovascular disease.

There are several studies that have associated US-CRP levels with the presence of CVD and atherosclerotic development [34], but there is limited research evaluating the ability of US-CRP to determine inflammation associated with CVD in HIV patients. The results of our study suggest that US-CRP may be as useful as ESR in reclassifying low or intermediate-risk patients who have not yet experienced cardiovascular events but may have subclinical CVD and could benefit from medical treatment adjustments.

The present study had several limitations. First, the small sample size decreased our ability to detect associations between CAC and analytical parameters; however, the careful selection of patients without cardiovascular risk factors and non-smoking patients made it possible to eliminate confounding factors. Nevertheless, it would have been useful to analyze clinical outcome as an endpoint in a larger sample, to prove the prognostic and clinical value of subclinical CVD progression. Second, after 6 years of follow-up, the appearance of classic cardiovascular risk factors was significant, which may be a confounding factor relating CAC to HIV-infection parameters. Third, the lack of a control group, or patients without HIV, could be considered a limitation of the present study. However, since the higher incidence of atherosclerosis among patients with HIV has been demonstrated in previous studies [10-12], and our aim was to determine which clinical and analytical parameters related to HIV were associated with the progression of subclinical atherosclerosis, we used the same population of patients with a > 10-year history of HIV specific techniques which are not commonly used in clinical practice to determine whether we were able to detect early. A 6-year follow-up of an HIV-positive cohort allowed us to study the association between clinical and analytical outcomes. In addition, the use of healthy HIV-negative subjects as controls must be weighed against the risk associated with radiation. Moreover, the benefits of MDCT, including cancer screening, must be balanced against the risk of radiation enhancement in HIV patients. However, more extensive follow-up would be desirable to be able to verify the long-term evolution.

CONCLUSIONS

In summary, the probably rapid progression of subclinical CVD in patients with HIV supports the use of MDCT and carotid CIMT to detect increased cardiovascular risk in HIV patients whose SCORE2 index may underestimate it. HIV-infected patients with a SCORE2 index close to a cut-off point for the initiation of treatment may also benefit from MDCT to determine CAC and MESA risk to address early cardiovascular risk-modifying factor management.

Further studies with larger populations and longer follow-up time are needed to assess whether the introduction of new non-invasive techniques such as MCDT and carotid ultrasound will improve the diagnosis of subclinical CVD and endothelial dysfunction in clinical practice in patients with HIV.

FUNDING

None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest

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Official journal of the Spanish Society of Chemotherapy

Original breve

Revista Española de Quimioterapia
doi:10.37201/req/117.2023

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Descriptivo de los casos de citomegalovirus congénitos en un hospital terciario entre 2017-2023

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Article history
Received: 27 September 2023; Revision Requested: 17 October 2023; Revision Received: 13 November 2023; Accepted: 29 November 2023; Published: 23 May 2024

RESUMEN

Introducción. La infección por citomegalovirus (CMV) es la infección congénita más frecuente en nuestro medio. El objetivo de nuestro estudio fue describir las características de los niños con infección congénita por CMV de un centro terciario en los últimos 6 años.

Material y métodos. Estudio descriptivo retrospectivo en el que se incluyeron todos los niños consecutivos identificados con diagnóstico de infección congénita por CMV atendidos en un hospital terciario de la Comunidad de Madrid entre los años 2017-2023.

Resultados. Se incluyeron 22 niños diagnosticados de CMV congénito. Un 54.5% presentaban diagnóstico prenatal de los cuales un 50% fue en el tercer trimestre, un 25% en el primero y 25% en el segundo. Un 22.7% fueron recién nacidos pretérminos (RNPT). En todos se aisló CMV en orina con carga viral (CV) elevada (mayor de 1000 copias/ml). Cuando se realizó CV en sangre, 11/22 (50%) presentaban CV elevada. Solo un paciente (de 21) presentó CV elevada en LCR. El 45% tenía afectación en la ecografía transfontanelar entre lo que destacaban vasculopatía lenticuloestriada (62%), hemorragia intraventricular (30%) o calcificaciones periventriculares (20%). Un 68% permanecieron asintomáticos. Al nacimiento fueron clasificados recién nacidos con crecimiento intrauterino retardado (CIR) un 20% o se objetivaron alteraciones clínicas o analíticas (neutropenia, plaquetopenia, colestasis). El 32% recibió tratamiento con valganciclovir. El 36% presentó secuelas, siendo las más frecuente hipoacusia (33%) y en un caso fallecimiento.

Conclusiones. La infección congénita por CMV sigue constituyendo un grave problema de salud pública presente en nuestro medio. Aunque, en la mayoría de casos, sean leves o asintomáticos, debemos tener alta sospecha clínica ante sintomatología o historia materna compatible y realizar un diagnóstico y tratamiento precoces, para evitar o disminuir las secuelas a largo plazo.

Palabras clave: Citomegalovirus congénito, clínica, diagnóstico, tratamiento

A descriptive overview of cases of congenital cytomegalovirus at a tertiary hospital between 2017 and 2023

ABSTRACT

Introduction. Cytomegalovirus infection (CMV) is the most common congenital infection in developed countries. The aim of our study was to describe the features of the children that have congenital CMV infection at our hospital for the last 6 years.

Material and methods. A retrospective descriptive study was designed that included all the children with CMV congenital infection that were diagnosed at tertiary hospital of Madrid Community between 2017 and 2023.

Results. Twenty-two children were included. 54.5% have a prenatal diagnosis, 50% of them were in the third trimester, 25% at first trimester and 25% at the second. 22.7% were preterm. CMV was isolated in all the samples with CV more than 1000 copies/ml. When CMV was made in blood, 11/22 (50%) had a high CV. Only one newborn had a high CV at CRL. 44% have affectation at transfontanellar ultrasound evidenced by vasculopathy (62%), intraventricular hemorrhage (IVH) or periventricular calcifications (20%). 68% were asymptomatic, al-

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though 20% had a retarded intrauterine growth (RIG) at birth or clinical features or analytical were objectified (neutropenia, thrombocytopenia, cholestasis). 33% got treatment with valganciclovir and 33% had sequelae (hearing loss).

Conclusions. CMV congenital infection is still a severe public health issue in developed countries. Most of the cases are mild or asymptomatic even though we should have high clinical suspicion with compatible symptoms and consistent maternal history in order to make an early diagnosis and treatment to prevent or reduce sequelae.

Keywords: Congenital cytomegalovirus, clinical, diagnosis, treatment

INTRODUCCIÓN

El citomegalovirus (CMV) es un virus ADN de la familia *Herpesviridae* y continúa siendo la infección congénita más frecuente en nuestro medio con una prevalencia entre 0,5-2% de los recién nacidos [1,2]. En la mayoría de los casos ocurre tras una primoinfección materna (1-4% de las gestantes) produciendo hasta en un 40% de estos casos una transmisión fetal, siendo más frecuente en el tercer trimestre aunque cursando con mayor gravedad si la infección ocurre en primer o segundo trimestre. Hasta el 90% de los recién nacidos serán asintomáticos, pero un 10-15% pueden tener secuelas a largo plazo o fallecer a causa del CMV [1-3].

El diagnóstico de sospecha habitualmente se realiza prenatalmente mediante serología materna que se puede confirmar mediante técnicas de biología molecular como reacción cadena de polimerasa (PCR) en líquido amniótico o en el momento neonatal en orina tanto en el recién nacido asintomático como en aquél con sospecha clínica: trombocitopenia, petequias, hepatoesplenomegalia, afectación del sistema nervioso central (SNC) (como microcefalia, sordera, coriorretinitis) o afectación ecográfica del SNC. Además, es recomendable realizar cribado mediante PCR en orina a los recién nacidos de madre que viven con VIH, prematuros (menores de 32 semanas), bajo peso (o < 1.500 g) o que presenten crecimiento intrauterino retardado (CIR) [1-6,8-10].

Hasta un 40% de los neonatos sintomáticos desarrollarán secuelas a largo plazo, siendo la más frecuente la sordera neurosensorial bilateral (60-75%) [1,4,6,8,9] por lo que es importante realizar un seguimiento prospectivo y multidisciplinar de estos pacientes de forma prolongada por la posibilidad de secuelas a largo plazo, incluso cuando no están presentes al nacimiento.

La indicación de tratamiento es controvertido en pacientes asintomáticos. Se recomienda la administración de valganciclovir oral (16 mg/kg/12h) durante 6 meses en aquellos recién nacidos con afectación del SNC, afectación multiorgánica o que presentan hipoacusia [1, 3-5]. Para la prevención de la infección congénita en mujeres que presentaban primoinfección demostrada en el embarazo, se ha utilizado como uso profiláctico gammaglobulina humana anti-CMV, basado en un primer estudio no aleatorizado donde se documentó infección congénita en el 16% de las mujeres que recibieron tratamiento con la gammaglobulina humana hasta el parto, frente al 40% que no recibió [10]. Un estudio posterior más amplio aleatorizado no demostró beneficio del uso de gammaglobulina humana anti-CMV [11]. El único tratamiento que ha resultado eficaz en la embarazada es el valaciclovir oral a dosis altas, que reduce la incidencia de infección congénita sintomática como demostró un amplio estudio abierto multicéntrico realizado en Francia [12].

Hoy en día, en nuestro país no hay datos de cuál es la prevalencia de la infección congénita en el recién nacido ya que solo ha sido estudiada en grupos de riesgo específicos, como en niños prematuros o hijos de madre que vive con VIH. Sin embargo, recientemente se ha realizado el primer estudio prospectivo de prevalencia del citomegalovirus congénito en Madrid, en el que se observó que 1 de cada 200 recién nacidos en el Hospital 12 de Octubre presentaban dicha infección. En la actualidad, en la Comunidad de Madrid, no se realiza cribado prenatal ni postnatal debido a la ausencia de vacuna y medidas preventivas que hayan demostrado ser coste-efectivas [13]

El objetivo de nuestro estudio fue describir las características de los niños con infección congénita por CMV de nuestro centro en los últimos 6 años.

MATERIAL Y MÉTODOS

Se diseñó un estudio descriptivo, observacional y retrospectivo en el que se incluyeron todos los casos de recién nacidos diagnosticados de CMV congénito del Hospital Clínico San Carlos, Madrid, entre 2017 y 2023.

Se consideró diagnóstico de CMV congénito presentar PCR positiva de CMV en orina en los primeros 15 días de vida. Se consideró CV elevada la detección > 1000 copias/ml. El neonato sintomático se definió como aquel con sintomatología o con hallazgos analíticos o ecográficos compatibles con infección congénita por CMV. Se consideró recién nacidos pretémino (RNPT) el menor de 37 semanas de edad gestacional. Se considera sintomatología compatible la hepatoesplenomegalia aislada, la microcefalia (PC < percentil 3), bajo peso al nacimiento (Peso < percentil 10 para edad gestacional) o CIR (Peso < percentil 3 para edad gestacional) y alteraciones en el SNC como sordera neurosensorial, coriorretinitis o hipotonía y letargia sin otra causa que lo justifique. Se consideró afectación analítica la presencia de trombocitopenia, hipertransaminasemia, hiperbilirrubinemia conjugada, anemia o leucopenia. Se describió afectación ecográfica como la presencia de calcificaciones periventriculares, vasculopatía o hemorragias intraventriculares, aunque estos hallazgos podrían estar en relación con la prematuridad.

Se recogieron variables epidemiológicas: infección durante el embarazo y trimestre en el que se produce el contagio; sexo, edad gestacional y peso al nacimiento. Se analizaron datos microbiológicos (PCR de CMV, carga viral (CV) en orina, sangre y líquido cefalorraquídeo), de imagen (afectación ecográfica o en resonancia magnética), así como las características clínicas y analíticas, el tratamiento recibido y el desarrollo de secuelas,

Tabla 1 **Características pacientes citomegalovirus congénitos**

Características demográficas	Mediana	RIC	
Edad gestacional	38 semanas	23-41 semanas	
Peso al nacimiento	2.920 g	840-3.980 g	
Sintomatología	Sintomáticos (n=7)	Asintomáticos (n=15)	Total (n=22)
Tratamiento	5	2	7
Secuelas	4	4	8

entendidas como tales la hipoacusia, el retraso psicomotor o alteraciones del SNC.

Cada paciente recibió un código numérico anónimo, siendo el único dato que lo identificaba y por tanto no fue necesario solicitar un consentimiento informado del paciente para este estudio.

Se han cumplido los preceptos éticos y legales necesarios para desarrollar este proceso de investigación: se ha recibido la aprobación por parte del Comité de ética e Investigación Clínica (CEIC) del Hospital Clínico San Carlos (Código Interno: 22/591) y se ha garantizado tanto la seguridad como la confidencialidad de los datos obtenidos de los pacientes a través del cumplimiento de la Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales, en vigor desde el 7 de diciembre de 2018.

En el estudio descriptivo, las variables cuantitativas con distribución no normal mediante la mediana y el rango intercuartílico (RIC). Para las variables cualitativas se han empleado frecuencias absolutas o relativas (%). En el análisis inferencial, para la realización de comparaciones entre variables cualitativas se ha utilizado la prueba exacta de Fischer.

RESULTADOS

Se diagnosticaron 22 pacientes con infección congénita por citomegalovirus (Tabla 1). En el 54,5% se realizó un diagnóstico prenatal (12/22), de los cuales el 25% fue en el primer trimestre (3/12), el 25% en el segundo trimestre (3/12) y el 50% en el tercer trimestre (6/12). La mediana de edad gestacional al nacimiento fue 38 semanas (RIC 25-41). El 22% de los pacientes de la muestra fueron RNPT. La mediana de peso al nacimiento fue 2.920 g (RIC 840-3.980 g).

Todos presentaron carga viral elevada en orina (mediana 1.000.000 copias/ml). El 50% (11/22) presentó CV elevada en sangre, con una mediana de 5628 copias/ml (RIC 153-20.000). Solamente en uno de los neonatos se detectó carga viral en líquido cefalorraquídeo (LCR) aunque fue realizado en 21 de los niños.

Se realizó ecografía transfontanelar en 19 de los recién nacidos. Solo un 45% tuvo afectación ecográfica (10/19). El principal hallazgo fue la vasculopatía, presente en un 50% (5/10) junto con hemorragia intraventricular grado I (3/10). En dos de estos pacientes (20%) se hallaron calcificaciones periventriculares o lenticulo-estriadas.

En lo referido a la sintomatología, el 68% de los neonatos estaban asintomáticos en el momento del diagnóstico (15/22). El 32% restante presentó sintomatología variada entre lo que se encontraba los siguientes síntomas clínicos: bradicardia (5%), fiebre (5%) o crecimiento intrauterino retardado tipo 1 (10%). En cuanto los hallazgos analíticos destacaron los siguientes: neutropenia (10%), plaquetopenia (10%) y colestasis (5%).

Respecto al tratamiento, 7/22 recibieron tratamiento (32%), 5 sintomáticos y dos asintomáticos debido a afectación extensa en ecografía. uno recibió ciclo durante 10 días con ganciclovir intravenoso y posteriormente valganciclovir durante 6 meses. el resto recibió tratamiento con valganciclovir exclusivamente durante 6 meses. Uno de ellos, además, requirió administración de factor estimulador de colonias.

Se documentaron secuelas en 8 de los 22 pacientes (32%), 4 de los pacientes sintomáticos y 4 asintomáticos, siendo la hipoacusia la secuela más frecuente (33%), 2 de los niños presentaron disminución de respuesta en potenciales visuales, 1 de ellos tenía hipertonía e hiperreflexia y 1 de los pacientes falleció en probable relación a prematuridad (RN de 32 semanas y 900 gr de peso al nacimiento).

DISCUSIÓN

La infección por CMV congénita sigue constituyendo un grave problema de salud pública en nuestro medio, siendo la infección congénita más frecuente [1], con sintomatología y secuelas en un porcentaje en torno a un 15-20%, similar a la descrita en otros países [9]. Sin embargo, no se ha establecido de rutina un cribado prenatal en nuestro país ni en la mayoría de países de la comunidad europea [8]. A pesar de ello, en nuestro estudio se muestra un elevado porcentaje de diagnóstico durante el embarazo, sobre todo en el primer trimestre, en probable relación al cribado que se realiza en posibles poblaciones de riesgo (sanitarias, contacto con niños en el trabajo, madres que viven con VIH) o en presencia de sintomatología compatible. En cuanto a la epidemiología, la mayor parte de los niños nacen a término, con bajo peso para edad gestacional,

siendo ésta una de las recomendaciones de cribado de CMV en la actualidad [1].

La PCR cualitativa y la cuantificación de carga viral en orina mediante PCR de CMV continúan siendo los métodos de elección para el diagnóstico de infección congénita de CMV en el neonato [1-5], debiendo realizarse en los 15 primeros días de vida. En nuestra serie, todos los niños presentaban PCR positiva y carga viral elevada en orina, al igual que en otras series [8], al ser criterio de inclusión como definición de CMV congénito. Además, se ha demostrado la utilidad de detección de carga viral en sangre que resultó elevada en la mitad de las muestras. En nuestra muestra, destaca la escasa utilidad de la extracción de LCR para estudio, dado que solamente uno de los pacientes mostraba CV en dicho medio. Aunque se ha sugerido que debería incluirse la punción lumbar como estudio de extensión y considerado como valor pronóstico, su uso es controvertido, pues no se ha asociado pronóstico en series amplias [14].

La PCR en orina, más allá de los 15 días de vida, no permite distinguir la infección congénita de la adquirida, por lo que, todos aquellos niños asintomáticos al nacimiento pueden pasar desapercibidos. El único método que se conoce hasta ahora para llevar a cabo un diagnóstico retrospectivo de la infección es mediante una PCR de la muestra de sangre del papel de filtro procedente del cribado neonatal de las enfermedades metabólicas, que adolece de baja sensibilidad.

En nuestra serie la mitad de los casos presentan afectación ecográfica. Además, estos hallazgos eran compatibles tanto con la infección como con la prematuridad de los niños de la muestra, tales como la hemorragia intraventricular o la vasculopatía inespecífica. Por tanto, los hallazgos encontrados no pueden correlacionarse completamente con la aparición de secuelas neurológicas en relación con la infección. De manera análoga ocurre con las secuelas y el fallecimiento, al tratarse de un recién nacido pretérmino de 32 semanas y 900 gramos de peso. A pesar de ello, la secuela más frecuente continúa siendo la hipoacusia, al igual que en el resto de series europeas [5,6,8,9].

El tratamiento empleado, se realizó siguiendo las recomendaciones establecidas [1-6]. En los casos que el paciente estaba ingresado cuando se realizó el diagnóstico se administró tratamiento intravenoso con ganciclovir. Aquellos diagnosticados de forma ambulatoria, en pacientes con secuelas como la hipoacusia, se pautó valganciclovir vía oral durante 6 meses, duración que ha demostrado mejorar la hipoacusia y el desarrollo neurológico comparado con pautas más cortas [5]. No se ha demostrado clara relación de las secuelas ni de la gravedad de las mismas con el tratamiento en nuestra serie, al contrario que en otras series europeas [8] que demuestran disminución de la gravedad de las secuelas en aquellos niños sintomáticos que reciben tratamiento.

Las características de nuestra muestra coinciden con lo publicado en la literatura sobre la clínica, las pruebas diagnósticas y el tratamiento: la mayoría de los recién nacidos son asintomáticos al nacimiento y no requieren tratamiento; la prueba de mayor rentabilidad diagnóstica es la PCR de CMV en orina en comparación con el resto de las muestras; la secuela más frecuente es la sordera y para el tratamiento de la infección en el recién nacido actualmente se utilizan dos fármacos: valganciclovir oral y de forma excepcional ganciclovir intravenoso.

En lo referente a las limitaciones de nuestro estudio, la validez externa se ve afectada ya que al tener un escaso tamaño muestral no podemos generalizar los resultados de la muestra estudiada a la población de referencia. Además, influye también las características del hospital terciario, que recibe madres y recién nacidos seleccionados de riesgo. Sumado a ello, su naturaleza retrospectiva no permite hacer cálculos sobre la prevalencia de la enfermedad ni valorar sus secuelas en la población general. Además, el carácter retrospectivo del estudio conlleva la pérdida de algunos datos en la recogida de distintas variables y las guías de seguimiento y terapéuticas han sufrido cambios en el tiempo.

En cuanto a la validez interna, la cohorte contiene una muestra homogénea, ya que todos fueron pacientes consecutivos que presentaron PCR positiva en orina en los 15 primeros días de vida. Además, el estudio recopila todos los casos diagnosticados en un centro de tercer nivel y permite conocer la presentación clínica y el abordaje terapéutico realizado. En nuestra serie, confirmamos que la infección congénita por CMV sigue constituyendo un grave problema de salud pública, con elevada morbimortalidad en el recién nacido afecto, y en cuyo abordaje se plantean importantes áreas de mejora. Hoy en día sigue sin existir una indicación clara de cribado gestacional o del recién nacido del citomegalovirus congénito, el cual se debería valorar ya que permitiría evaluar y diagnosticar de forma oportuna y precoz a los recién nacidos y considerar la necesidad de tratamiento. Se deberían realizar estudios a mayor escala que causen impacto y permitan así la toma de decisiones de salud pública. El desarrollo de vacunas eficaces y seguras frente a la infección por CMV es una prioridad. Existen candidatas en estado avanzado, que podría ser esenciales en la prevención de la infección en mujeres seronegativas en edad fértil, y evitar así el contagio durante el embarazo, situación de máximo riesgo de transmisión de CMV congénito [16]

AGRADECIMIENTOS

A la Dra. Esther Culebras, del Servicio de Microbiología del HCSC por el apoyo continúo, así como inestimable ayuda en la determinación y cuantificación de muestras

FINANCIACIÓN

Los autores declaran que han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

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Official journal of the Spanish Society of Chemotherapy

Brief report

Revista Española de Quimioterapia
doi:10.37201/req/028.2024

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Exploring therapeutic options for mild diabetic-related foot infections: a comparative *in vitro* study of cefditoren versus amoxicillin/clavulanic acid

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Article history
Received: 15 April 2024; Revision Requested: 9 May 2024; Revision Received: 17 May 2024; Accepted: 27 May 2024; Published: 13 June 2024

ABSTRACT

Skin and soft tissue infections (SSTIs), and particularly diabetic-related foot infections (DFI), present diagnostic and therapeutic complexities, often leading to severe complications. This study aims to evaluate the *in vitro* efficacy of cefditoren and amoxicillin/clavulanic acid against typical DFI pathogens. Clinical samples from 40 patients with mild SSTIs were analyzed, revealing a predominance of *Staphylococcus* spp. and *Streptococcus* spp. species. Cefditoren exhibited activity against 90% of isolates, with superior potency over amoxicillin/clavulanic acid. These findings underscore the utility of cefditoren in empirical treatment of DFI, although a larger sample size would be desirable for further validation.

KEYWORDS: Cefditoren; amoxicillin/clavulanic acid, diabetic foot infections, mild,

Alternativas terapéuticas en la infección leve del pie de diabético: estudio comparativo *in vitro* de cefditoreno frente a amoxicilina/ácido clavulánico

RESUMEN

Las infecciones de piel y partes blandas (IPPB), y en particular las infecciones del pie de diabético (IPD), presentan complicaciones diagnósticas y terapéuticas, que a menudo desembocan en complicaciones graves. El objetivo de este estudio fue evaluar la eficacia *in vitro* de cefditoreno y amoxicilina/ácido clavulánico frente a los microorganismos típicos de las IPD. Se analizaron muestras clínicas de 40 pacientes con IPPB leves mostrando un predominio de especies de *Staphylococcus* spp. y *Streptococcus* spp. Cefditoreno mostró frente al 90% de los aislados una potencia superior a la de la amoxicilina/ácido clavulánico. Estos resultados destacan la utilidad de cefditoreno en el tratamiento empírico de la IPD, aunque sería deseable disponer de un mayor tamaño muestral para una mejor validación.

PALABRAS CLAVE: Cefditoreno; amoxicilina/ácido clavulánico, infecciones del pie diabético, leve

INTRODUCTION

Skin and soft tissue infections (SSTIs) are common conditions involving a wide range of physiological structures with varying severity and prognosis [1,2]. Among them, diabetes-related foot infection (DFI) represents a diagnostic and therapeutic challenge [3]. DFIs are complex and debilitating consequences of diabetes mellitus. Diabetic neuropathy, peripheral artery disease and immune dysfunction predispose the foot to injury and exacerbation of bacterial infections [4]. Currently, DFI is the most common cause of lower extremity amputation and the most common reason for prolonged hospitalization for diabetic patients with high socioeconomic implications for patients and health systems [5-9]. Treatment of DFI requires a multidisciplinary approach and tailoring of antibiotic therapies to the causative pathogen to improve efficacy and reduce antimicrobial resistance [10]. Methicillin-susceptible *Staphylococcus aureus* (MSSA) and other Gram-positive cocci are predominant in DFIs without deep tissue involvement or systemic signs (mild infections) [10,11]. Therefore, DFI guidelines recommend oral amoxicillin-clavulanic acid as the first choice for empirical treatment of mild infections in patients with no history of MRSA infection or colonization and without recent hospitalization [10].

Cefditoren pivoxil, a third-generation cephalosporin exhibits promising activity against common DFI pathogens [12,13], making it a potential first-line treatment option.

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The aim of this study was to evaluate the antimicrobial activity of cefditoren against pathogens recovered from mild DFIs of patients requiring, at least initially, oral treatment.

METHODS

A prospective study was conducted to assess the antibiotic susceptibility of DFI bacterial isolates to amoxicillin-clavulanic acid and cefditoren. Clinical isolates from consecutive samples (tissue biopsies) collected between November 2023 and March 2024 from outpatients with mild DFIs treated in our teaching hospitals were analyzed. DFIs were classified as mild according to the depth and extent of the wound as defined by the Infectious Diseases Society of America guidelines [10]. Isolates were identified in the bacteriology laboratory using standard operating procedures after homogenization of the samples. Routine testing of penicillin and cefoxitin susceptibility was performed [14,15]. All isolates were stored at -80°C and subsequently used for broth microdilution susceptibility testing to amoxicillin-clavulanic acid and cefditoren according to CLSI recommendations [14]. MIC values were determined after 18-20 hours of incubation at 37°C in ambient or 5% CO_2. Interpretation of antimicrobial susceptibility for amoxicillin-clavulanic acid was performed using current EUCAST breakpoints and recommendations [15]. For staphylococcal species and *Streptococcus* group B isolates, susceptibility was inferred from cefoxitin and penicillin results respectively [15]. For *Streptococcus viridans* groups strains, a MIC≤0.12 mg/L was used as interpreting criteria. For cefditoren, susceptibility breakpoints based on pharmacodynamic data, ranging from ≤0.125 mg/L (FDA prescribing information) to ≤0.5 mg/L (approved by the reference Member State, Spain, during the Mutual Recognition Procedure in Europe) for community respiratory pathogens, or MIC ≤ 1 mg/L for non-respiratory pathogens were applied [13,16].

RESULTS

A total of 40 tissue specimens were received during the study period. All specimens were culture-positive and 34 showed the growth of a single microorganism. Six specimens were polymicrobial, yielding 2 to 3 microorganisms each. In total, 47 aerobic microorganisms were isolated (Table 1). In 27 out of 40 (67.5%) specimens, the isolated species was *S. aureus*; being 85.5% of them (23 out of 27) methicillin-susceptible with 78.3% (18 out 23) isolated in pure culture. In 4 out of 40 (10%) specimens, MRSA was the recovered isolate (8.5% of all microorganisms). Other species of staphylococci were recovered from 8 out of 40 (20.0%) specimens, including 4 *S. epidermidis* isolated in pure culture, 2 *S. lugdunensis* and 3 other coagulase-negative staphylococci, accounting for 19.1% (9 of 47) of all isolates. *Streptococcus* species were isolated from 11 of 40 (27.5%) specimens, representing 23.4% of total isolates (11 out of 47), with *S. agalactiae* as the most predominant streptococci.

Table 1 Distribution of isolated microorganisms

Microorganisms	No. isolates n=47	% total isolates	% within the genus	No. in pure culture n=34
Staphylococcus spp.	36	76.6		26
S. aureus	27	57.5	75.0	22
MSSA	23	48.9	63.89	18
MSRA	4	8.5	11.11	4
S. haemolyticus	1	2.1	2.78	-
S. epidermidis	4	8.5	11.11	4
S. lugdunensis	2	4.2	5.56	-
Other Staphylococci	2	4.2	5.56	-
Streptococcus spp.	11	23.4		8
S. agalactiae	7	14.9	63.64	6
salivarius group	2	4.2	18.18	1
anginosus group	2	4.2	18.18	1

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2 MIC_{50}, MIC_{90} and MIC range for cefditoren and amoxicillin-clavulanic acid (mg/L)

	Cefditoren		Amoxicillin/clavulanic acid	
Microorganism	MIC_{50}/ MIC_{90}	Range	MIC_{50}/ MIC_{90}	Range
S. aureus	0.12/0.25	0.12-0.25	0.5/1	0.12-1
S. epidermidis	0.06/0.12	0.06-0.12	0.5/0.5	0.25-0.5
S. lugdunensis	0.06/0.12	0.06-0.12	0.5/0.5	0.5
S. haemolyticus	0.5/0.5	0.5	2/2	2
Other staphylococci	0.03/0.06	0.03-0.06	0.12/0.12	0.12
***Staphylococcus* spp.**	**0.12/0.25**	**0.12-0.5**	**0.5/1**	**0.12-2**
S. agalactiae	0.007/0.015	0.007-0.015	0.015/0.015	0.015
S. anginosus	0.007/0.015	0.007-0.015	0.015/0.12	0.015-0.12
S. salivarus	0.015/0.015	0.015	0.06/0.06	0.06
Streptococcus spp.*	**0.015/0.015**	**0.007-0.015**	**0.015/0.12**	**0.015-0.12**

*All isolates were penicillin-susceptible

The antimicrobial susceptibilities of the microorganisms isolated, excluding MRSA strains, are shown in Table 2. All staphylococci and streptococci strains tested were fully susceptible to amoxicillin-clavulanic acid and cefditoren with MICs ranging from 0.015-2 mg/L and 0.007-0.5 mg/L respectively. The MIC_{90} for cefditoren were 4-8 folds lower than those for amoxicillin-clavulanic acid.

DISCUSSION

Skin and soft tissue infections (SSTi) represent a significant burden on healthcare systems, particularly among persons with diabetes, who have predisposition to these complications due to their comorbidities [5,7,9]. The present study offers insights into the bacterial aetiology of diabetes-related superficial infections and highlights the activity of cefditoren against the isolated microorganisms, making it a potential therapeutic option for the management of this condition.

These findings underscore the predominance of S. *aureus* as the primary causative agent in early DFIs, consistent with previous reports emphasizing the significance of this microorganism in SSTIs [17,18]. Notably, most of the *S. aureus* isolated were susceptible to methicillin supporting beta-lactams with approved clinical indications for staphylococcal infections, as first-line agents for the treatment of mild DFIs.

Cefditoren has the indication for the treatment of uncomplicated SSTIs, but susceptibility breakpoints have not been defined to guide dosing in clinical practice. However, due to the unreliability of staphylococcal breakpoints, the International Committees on Antimicrobial Susceptibility Testing have decided to eliminate all breakpoints for anti-staphylococcal β-lactams, except penicillin, oxacillin, cefoxitin, and ceftaroline [14,15]. Current guidelines encourage laboratories to interpret susceptibility to beta-lactams using penicillin, oxacillin, or cefoxitin as surrogates [14,15].

This study demonstrates that cefditoren exhibits similar coverage to amoxicillin-clavulanic acid against common DFI pathogens (91.5%) but with 4 to 8 times greater antimicrobial potency. The acceptable case coverage threshold (90%), in line with the percentages of efficacy that cefditoren has previously demonstrated in SSTIs [12,13], makes it an optimal candidate for the empirical treatment of patients with mild DFIs. Studies involving a larger number of specimens are warranted.

In conclusion, our study sheds light on the microbial landscape and susceptibility patterns of SSTI in persons with diabetes and provides microbiological evidence supporting the clinical efficacy of cefditoren against SSTI common pathogens in published studies [12,13], emphasizing its microbiological adequacy for empirical treatment of DFI.

FUNDING

This study was funded by Meiji Pharma Spain (MPS).

CONFLICTS OF INTEREST

P. Coronel and E. Gómez-Rubio are employees of Meiji Pharma Spain. Rest of authors have no conflict of interest.

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Official journal
of the Spanish Society
of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/139.2023

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Meningitis bacteriana por *Streptococcus gallolyticus* subespecie *pasteurianus* en paciente adulto: revisión de la literatura

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Article history
Received: 26 November 2023; Revision Requested: 2 January 2024; Revision Received: 11 June 2024; Accepted: 17 June 2024; Published: 20 June 2024

Estimado Editor:

La meningitis causada por *Streptococcus gallolyticus* subespecie *pasteurianus (S. gallolyticus* subsp. *pasteurianus)* está bien descrita en la población pediátrica, sobre todo en la etapa neonatal [1]. Sin embargo, es poca la literatura acerca de su presentación en adultos [1,2]. Presentamos un caso clínico con el que queremos poner de manifiesto la rareza de esta entidad en adultos y, seguidamente, realizar una revisión bibliográfica sobre la misma.

Se presenta el caso de un varón de 41 años, natural de Colombia, que acudió al servicio de urgencias por fiebre de 39ºC y alteración del nivel de consciencia (con 5 puntos en la escala de coma de Glasgow). Como único antecedente de interés, el paciente presentaba un hábito enólico importante los fines de semana. A la exploración se apreciaba un mal estado general y los signos meníngeos eran positivos. Se realizó una tomografía computerizada craneal sin contraste en la que no se objetivaron hallazgos patológicos. Se completó el estudio con la extracción de hemocultivos, analítica sanguínea y la realización de una punción lumbar con salida de líquido cefalorraquídeo (LCR) de aspecto turbio. El análisis de los resultados del LCR eran sugestivos de una meningitis aguda bacteriana: pleocitosis con 18029 leucocitos/mm^3 con predominio (70%) polimorfonuclear (PMN), 338 hematíes/mm^3, proteinorraquia de 413 mg/dl y glucorraquia < 10 mg/dl. Asimismo, en la analítica sanguínea destacaba: leucocitosis de 24390/mm^3 con un 93% de PMN, glucemia de 164 mg/dl, lactato de 3,36 mmol/L, procalcitonina 22,64 ng/ml y una proteína C reactiva de 158,9 mg/L.

Aunque no se dispuso de las concentraciones de lactato en LCR, la leucorraquia con predominio de PMN, la leucocitosis y la elevación de reactantes de fase aguda (sobre todo la procalcitonina) orientaban a una etiología bacteriana dado que todos ellos son factores independientes y, además, con mayor capacidad predictiva de esta etiología [3]. Por ello, se inició tratamiento antibiótico empírico con ceftriaxona 2 g/12 h, vancomicina 1 g/8 h y ampicilina 2 g/4 h, junto con dexametasona 8 mg/8 h. El paciente fue ingresado en la Unidad de Cuidados Intensivos.

El resultado de la PCR múltiple FilmArray en LCR fue negativo por lo que se mantuvo el tratamiento empírico inicial a la espera del resultado del cultivo. El enfermo presentó una muy buena evolución clínica y quedó asintomático ya en las primeras 48 horas. A las 72 horas se comunicó desde el servicio de microbiología el aislamiento tanto en LCR como en los hemocultivos de *S. gallolyticus* subsp. *pasteurianus*. Tras el resultado del antibiograma se desescaló el tratamiento manteniendo únicamente la ceftriaxona hasta completar un total de 14 días.

Dado el aislamiento de *S. gallolyticus* se completó el estudio con una colonoscopia y una ecografía abdominal que descartaron patología tanto a nivel hepatobiliar como colónica. Además, se realizó una ecocardiografía transtorácica con el fin de descartar una posible endocarditis infecciosa concomitante, en la que no se evidenciaron datos sugestivos de la misma. Finalmente, el paciente fue dado de alta tras completar la pauta antibiótica.

A raíz de este caso clínico, se ha realizado una revisión de la literatura de *S. gallolyticus* subsp. *pasteurianus* como agente etiológico de meningitis en pacientes adultos. Así, de los 65 casos de infección del sistema nervioso central (SNC) por *S. gallolyticus* encontrados, únicamente 8 de ellos fueron diagnosticados de meningitis aguda causadas por la subespecie *pasteurianus* [1,2,4]. En todos ellos, el LCR presentaba características típicas de infección bacteriana del SNC con pleocitosis de predominio PMN, proteinorraquia elevada e hipoglucorraquia. Sin embargo, solo en cuatro de ellos se consiguió aislar el patógeno en el LCR [2,5,6,7].

Aunque está bien descrita la asociación de este microorganismo con otras infecciones como la endocarditis infecciosa, únicamente se han descrito dos casos con afectación a este nivel [2,6].

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Asimismo, clásicamente se ha relacionado a *S. gallolyticus* con enfermedad hepática o gastrointestal, aunque solo un caso de los ocho se asoció a pólipos adenomatosos y en otra ocasión con antecedentes de estrongiloidiasis [6,8]. Por otra parte, en tres casos se describieron alteraciones digestivas (proctitis rádica, hemorroides y diverticulitis) no relacionadas con *S. gallolyticus*, en dos no se confirmó otras enfermedad y en uno no se realizó ningún estudio para descubrir una posible enfermedad digestiva asociada [1,2,4,8,9].

Finalmente, en cuatro de los ocho casos se describieron factores inmunomoduladores que condicionaban cierto grado de inmunosupresión a estos pacientes y que, por tanto, se podrían considerar factores de riesgo o predisponentes para la misma. Estas situaciones eran la esplenectomía, el tratamiento quimioterápico o con corticoides [2,5,8,9].

En conclusión, *S. gallolyticus* subsp. *pasteurianus* es una causa excepcional de meningitis en pacientes adultos. Únicamente se han publicado ocho casos, aunque en todos ellos la forma de presentación clínica y las características analíticas (sanguíneas y en el LCR) fueron muy sugestivas de etiología bacteriana [1,2]. Sin embargo, la clásica asociación con patología digestiva o la endocarditis no es un hallazgo constante [1,2]. No están claros los posibles factores predisponentes, aunque sí se ha observado que hasta en la mitad de los casos existen factores inmunomoduladores que podrían estar involucrados. En nuestro caso, el único factor que podría tener un papel inmunomodulador sería el hábito enólico, tal y como se ha descrito en alguna serie de casos en los que coincide una mayor tasa de hábito enólico con la infección por *S. gallolyticus* subsp. *pasteurianus* [10].

FINANCIACIÓN

Las autoras declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Las autoras declaran no tener conflictos de intereses

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/153.2023

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Evolución de los serotipos de *Salmonella* spp y su sensibilidad antibiótica en el Departamento de Salud Castellón

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Article history
Received: 31 December 2023; Revision Requested: 5 February 2024; Revision Received: 11 April 2024; Accepted: 17 April 2024; Published: 22 May 2024

Estimado Editor:

Salmonella spp. se clasifica en serotipos en base a la caracterización de sus antígenos somáticos y flagelares. Es conocido que la incidencia de las infecciones causadas por los diferentes serotipos varía mucho de unas regiones a otras debido a las diferencias culturales, a las prácticas de producción de alimentos, la ubicación geográfica y el nivel de desarrollo económico [1,2]. Con el objetivo de conocer la epidemiología de las gastroenteritis causadas por *Salmonella* spp. en nuestro Departamento de Salud y su sensibilidad antibiótica, estudiamos la evolución de sus serotipos durante un periodo de 30 meses incluyendo el año posterior a la fecha en la que se decretó el estado de alarma para hacer frente a la COVID-19.

Se recogieron variables sociodemográficas y microbiológicas de todos los casos, tanto esporádicos como asociados a brotes, con aislamiento de *Salmonella* spp en todas las heces a las que se les solicitó coprocultivo (una cepa por episodio) del 16 de septiembre de 2018 al 15 de marzo de 2021. El estudio de sensibilidad se realizó mediante el sistema automatizado VITEK-2 (bioMérieux) y la serotipificación de las cepas se llevó a cabo en el Instituto de Salud Carlos III según el esquema de Kauffmann-White-Le Minor [3]. Se compararon los casos de antes y después del inicio del confinamiento (14 marzo 2020). Todos los cálculos estadísticos se realizaron con el programa Stata® versión 14.

Durante el periodo de estudio se identificaron 272 casos de salmonelosis. La edad media de los pacientes fue de 21,8 años y el grupo de edad más prevalente fue el de <5 años (32%). Precisaron ingreso hospitalario el 14,3% de los enfermos. Los hombres (OR=3,14 95% IC 1,39-7,10), p=0,006, y los pacientes de mayor edad (OR=1,039 95% IC 1,02-1,05), p=0,000, fueron los que presentaron más riesgo de ser hospitalizados.

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Se identificaron 33 serotipos diferentes, siendo los más frecuentes: 1,4,[5],12:i:-, variante monofásica de Typhimurium, (43%), Enteritidis (29%), Montevideo (7,4%) y Typhimurium (3,7%). A lo largo del tiempo de estudio, se apreció una tendencia al aumento de casos de Enteritidis y a la disminución de casos de 1,4,[5],12:i:- que fue significativa (coeficientes de Spearman 0,202, p=0,001 y -0,130 p=0,032, respectivamente). La comparación de la distribución de los cuatro serotipos más frecuentes por edad y sexo solo mostró asociación estadística entre tener menor edad y padecer una salmonelosis causada por 1,4,[5],12:i:- (χ^2=14,62 p=0,0001).

En cuanto al estudio de sensibilidad, los porcentajes de sensibilidad global encontrados fueron: ampicilina 52,2%; amoxicilina/ácido-clavulánico 65,1%; ciprofloxacino 97,4%; cotrimoxazol 91,2%; cefotaxima 99,3%; e imipenem 100%. Presentaron resistencia a uno o más de estos antimicrobianos

Tabla 1 **Comparación de las características sociodemográficas y microbiológicas entre los periodos pre y post inicio del confinamiento**

	Pre-confinamiento	Post-confinamiento	p
Nº de casos	215	57	
Casos/día	0,42	0,16	
Edad media pacientes (años)	19,9	29	0,011
Sexo pacientes (%H/%M)	51,6%/48,4%	61,4%/38,6%	NS
Pacientes hospitalizados (%)	12,1%	22,8	0,04
Edad media hospitalizados (años)	37,9	56,1	0,001
Serotipos	26	15	
Sensibilidad ampicilina	46,5%	73,7%	0,000
Sensibilidad ciprofloxacino	98,6%	93%	0,037

Tabla 2 **Distribución de todos los serotipos en dos etapas: pre y post inicio del confinamiento**

Tipo	Pre-confinamiento n (%)	Post-confinamiento n (%)	Total n (%)
Agbeni	1 (0,5)		1 (0,4)
Albany	1 (0,5)		1 (0,4)
Ank	1 (0,5)		1 (0,4)
Blukwa		1 (1,8)	
Bovismorbificans	1 (0,5)	2 (3,5)	3 (1,1)
Braenderup	1 (0,5)		1 (0,4)
Brandenburg	3 (1,4)		3 (1,1)
Bredeney		1 (1,8)	1 (0,4)
Chester	3 (1,4)		3 (1,1)
Coeln	1 (0,5)		1 (0,4)
Cotham	1 (0,5)		1 (0,4)
Derby	1 (0,5)		1 (0,4)
Diarizonae	1 (0,5)	1 (1,8)	2 (0,4)
Salmonella enterica subsp salamae II	1 (0,5)		1 (0,4)
Enteritidis	50 (23,3)	29 (50,9)	79 (29)
Goldcoast	1 (0,5)	1 (1,8)	2 (0,7)
Hadar	1 (0,5)		1 (0,4)
Houston		1 (1,8)	1 (0,4)
Infantis	3 (1,4)		3 (1,1)
Kapemba		1 (1,8)	1 (0,4)
Mikawasima	3 (1,4)	1 (1,8)	1 (0,4)
Montevideo	19 (8,8)	1 (1,8)	20 (7,4)
Muenchen	1 (0,5)		1 (0,4)
Napoli	1 (0,5)		1 (0,4)
Newport		1 (1,8)	1 (0,4)
Poona	2 (0,9)		2 (0,7)
Rissen	3 (1,4)		3 (1,1)
Saintpaul	2 (0,9)		2 (0,7)
Salamae		1 (1,8)	1 (0,4)
Spartel	1 (0,5)		1 (0,4)
Stanley		1 (1,8)	1 (0,4)
Typhimurium	7 (3,3)	3 (5,3)	10 (3,7)
1,4,(5),12:i:-	105 (48,8%)	12 (21,1)	117 (43)
Total	215	57	272 (100)

el 89,7% de las cepas de *S.* 1,4,[5],12:i:-, el 7,6% de *S.* Enteritidis, el 10% de *S.* Montevideo y 70% de *S.* Typhimurium.

La comparación de las variables sociodemográficas y microbiológicas de los casos de antes y después del inicio del estado de alarma se muestra en la tabla 1. Hasta el 14 de marzo de 2020 los serotipos más frecuentes fueron 1,4,[5],12:i:- (48,8%), Enteritidis (23,3%), Montevideo (8,8%) y Typhimurium (3,3%); y después de esa fecha, Enteritidis (50,9%), 1,4,(5),12:i:- (21,1%), Typhimurium (5,3%) y Bovismorbificans (3,5%) (tabla 2). La proporción de casos debidos al serotipo 1,4,[5],12:i:- disminuyó más de la mitad en el segundo periodo (p=0,000) y la de Enteritidis aumentó más del

doble (p=0,000). La significación estadística se mantuvo tras ajustar por edad y sexo (p=0,001 para el serotipo 1,4,[5],12:i:-, p=0,000 para Enteritidis).

Aunque tener conocimiento acerca de los serotipos de *Salmonella* spp. circulantes en una región se considera un paso previo necesario para lograr su control, en nuestro país los estudios epidemiológicos actualizados sobre salmonelosis son escasos y, además, la mayoría no presentan la serotipificación completa de sus cepas [4-6]. En nuestro Departamento, el serotipo 1,4,[5],12:i:- es el más prevalente, y el porcentaje que representa es mucho mayor que el de otras series de distintos países [7-9]. El principal reservorio de este serotipo es el cerdo y, al parecer, en España esta variante monofásica es muy prevalente [10] tanto en los animales vivos como en sus carcasas; además, el consumo de productos porcinos es muy elevado en nuestro entorno.

A partir del inicio del estado de alarma se aprecian cambios en la epidemiología de la salmonelosis de nuestro Departamento: los pacientes: son significativamente más mayores; aumenta el porcentaje de pacientes hospitalizados y la edad de los mismos; el serotipo más frecuente pasa a ser Enteritidis (probablemente porque no pudieron seguirse determinadas costumbres y tradiciones alimentarias durante ese periodo); y, por último, aumenta la sensibilidad frente a ampicilina a expensas de la disminución de cepas de la variante monofásica y el aumento de Enteritidis. Pensamos que la oportunidad de comparar las variables sociodemográficas y microbiológicas analizadas entre el periodo pre-confinamiento y el posterior pone de manifiesto cómo las circunstancias excepcionales que rodean una pandemia pueden afectar a la evolución de otra enfermedad infecciosa ya endémica en una población.

CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

FINANCIACIÓN

No se ha recibido financiación para la realización del estudio

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/005.2024

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Detección del virus de Epstein-Barr en úlceras genitales femeninas

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Article history
Received: 9 January 2024; Revision Requested: 2 April 2024; Revision Received: 29 April 2024; Accepted: 1 May 2024; Published: 21 May 2024

Estimado Editor:

El virus de Epstein-Barr (VEB) es un herpesvirus linfotrópico que infecta al 90% de la población humana. Tras la primoinfección el virus persiste de forma latente en el interior de los linfocitos B y células epiteliales de la orofaringe, excretándose de forma irregular por la saliva [1,2].

La deteccion del VEB en las secreciones genitales de ambos sexos parece sugerir que, aunque la principal ruta de transmision es la oral, la difusion sexual directa puede producirse en los adolescentes. Los bajos niveles del VEB detectados en el territorio genital hacen pensar en que su único tipo celular de latencia son los linfocitos estromales tipo B [1,2].

Las úlceras genitales causadas por el VEB son una entidad poco frecuente, de este modo entre 1913 y 2013 sólo se han descrito 33 casos en mujeres, aceptándose que en estos casos el virus puede ser el causante directo de estas lesiones [3,4]. Debido a la escasa información sobre la detección o participación del VEB en las úlceras genitales de la población femenina, se ha realizado un estudio prospectivo sobre la etiología viral de este tipo de lesiones.

Desde julio hasta diciembre de 2023 se estudió prospectivamente la presencia de cualquier virus en las úlceras genitales femeninas de pacientes que acudieron al CAITS (Centro de Atención a las Infecciones de Transmision Sexual). Las muestras se remitieron en un medio de transporte para virus (Transport Medium, Vircell, Granada, Spain) y la detección viral se realizó mediante una PCR múltiple en tiempo real (Allplex Neurotropic Viruses; Seegen; South Korea) que detecta de forma simultánea y diferencial 12 virus distintos.

Durante el período de estudio se analizaron 264 muestras tomadas de las úlceras genitales. En ellas, 122 se consideraron como positivas (con presencia de algún virus), lo que reprresenta el 46,2%. En la Tabla 1 se exponen los virus detectados y su porcentaje de positividad. El herpesvirus simple tipo 2 (HSV-2) representó el 60,8% de todos los herpes (70/115 casos) y el herpes simple tipo 1 (HSV-1) el 39,2% (45/115 casos). El VEB se detectó en 14 muestras, es decir el 11,4% de todas las muestras positivas y el 5,3% del total de muestras analizadas. De los 14 VEB detectados, 7 (50%) lo fueron en solitario y 7 (50%) en coinfección con un herpesvirus; de ellos 6 (85,7%) con el HSV-1 y 1 (14,3%) con el HSV-2. El rango de edad de las mujeres con el VEB fue de 18-46 años (edad media 32 años); en 3 casos (21,4%) estaban infectadas por el virus de la inmunodeficiencia humana.

Las úlceras causadas por el VEB se caracterizan por ser profundas, dolorosas, únicas o múltiples de 0.5 a 2 cm de diámetro, de color rojo violáceo y de bordes irregulares; a pesar de ellos son muy difíciles de diferenciar de las causadas por los otros herpesvirus [4].

La presencia del VEB en las lesiones genitales podría deberse a dos posibilidades. En primer lugar, que las células epiteliales de este territorio se infectaran a través de la llegada de linfocitos B con latencia viral procedentes de la orofarige. Esta posibilidad se realizaría a través de las actividases sexuales orogenitales o digitogenitales, de modo que parte de la saliva infectada llegara a este teritorio [5]. A favor de esta hipótesis están nuestros datos que demuestras que en las coinfecciones el VHS-1 es el predominannte (85,7%), probablemente procedente de reactivaciones orofaríngeas y su transmisión a través de la saliva en las relaciones sexuales. La existencia de alguna pequeña herida o abrasión favorecería el desarrollo de la úlcera genital, ya que en cultivos celulares se ha podido observar como el VEB es capaz de infectar las células epiteliales de la mucosa vaginal [6]. A pesar de ello parece que las relaciones sexuales no son siempre un requisito para el desarrollo de las úlceras genitales, ya que en el estudio de Taylor *et al.* [6] el 50% de los casos no se había producido. En estos casos se postula que la diseminación sanguínea de linfocitos B infectados

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Tabla 1 **Detección de los diferentes virus en las úlceras genitales (n=122)**

Virus	No.de casos	(%)
Herpes simple tipo 2	68	55,7
Herpes simple tipo 1	38	31,1
HSV-1+HSV-2	2	1,6
Virus de Epstein-Barr	7	5,6
HSV-1+VEB	6	4,9
HSV-2+VEB	1	0,8

a la mucosa genital, determinaría el proceso patológico [6,7].

La segunda posibilidad es que el VEB se transmita también por vía sexual, especialmente en la adolescencia; este supuesto se apoyaría en la presencia del virus en el semen de personas con primoinfección [1,5]. Aunque esta posibilidad queda descartada en nuestro estudio dado que la edad media de las pacientes las aleja bastante de la primoinección por el VEB.

En el estudio de Staykova *et al.*[2] sobre la detecciòn de diferentes virus en las secreciones vaginales de mujeres asintomáticas detectan la presencia del VEB en el 9,6% de ellas. En pacientes positivas frente al VIH la prevalencia se situaría entre el 10-20%; a pesar de ello no se ha encontrado ninguna relacion con el desarrollo de lesiones cervicales [8]. Nuestro porcentaje de mujeres con el VEB e infección por el VIH es del 21,4%, que estaría en el rango superior de lo comunicado en este estudio.

Las técnicas de amplificación genómica permiten la detección de virus no esperables en diferentes muestras. La detección del VEB en las úlceras genitales femeninas abre la puerta a la realizacion de amplios estudios para conocer la participación patológica de este virus en este tipo de lesiones.

CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

FINANCIACIÓN

Los autores declaran que han recibido financiación para la realización de este estudio.

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/025.2024

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Bacteriemia producida por *Enterocloster aldenensis* en un paciente oncológico

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Article history
Received: 23 February 2024; Revision Requested: 5 April 2024; Revision Received: 8 April 2024; Accepted: 17 April 2024; Published: 17 May 2024

Estimado Editor:

Enterocloster aldenensis es un bacilo grampositivo anaerobio descrito inicialmente como *Clostridium aldenense* por Warren *et al.* [1], siendo posteriormente reclasificado como *E. aldenensis* por Haas y Blanchard [2]. Hasta el momento, solo existe un caso documentado de bacteriemia por *Enterocloster clostridioformis*, junto con *Eggerthella lenta* y *Dialister micraerophilus* [3]. Recientemente hemos observado un caso de bacteriemia debida a *E. aldenensis* aislado en cultivo puro en un paciente oncológico. En nuestro conocimiento, este es el primer caso de bacteriemia por este microorganismo aislado en cultivo puro.

Hombre de 62 años con antecedentes de cirugía previa por perforación colónica (1 mes antes) y lesión expansiva cerebral de localización fronto-parietal izquierda, que acude a urgencias por un episodio convulsivo que solo requirió aumento de dosis de dexametasona. Además, el paciente fue diagnosticado de forma concomitante de una eventración completa por una laparotomía previa, siendo sometido a cirugía reparadora con injerto, en el que no se observó daño intestinal. En la exploración física se observó una presión arterial de 90/50 mmHg, frecuencia cardiaca de 90 lpm, taquipnea (30 rpm) y fiebre de 38.5ºC. La analítica de sangre al ingreso mostró niveles elevados de glucosa (275 mg/dL), proteína C reactiva (7,5 mg/dL) y leucocitos (18.600/mm^3). Se obtuvieron 2 tomas de hemocultivos de sangre periférica y se enviaron al laboratorio de microbiología para su procesamiento, a la vez que se instauró tratamiento empírico con meropenem (1 g/8 h). Los frascos de hemocultivos fueron incubados en el sistema de monitorización continua BACTEC FX 40 (Becton Dickinson, Franklin Lakes, NY). A las 24 h de incubación, los dos frascos anaerobios resultaron positivos; las muestras fueron subcultivadas en agar sangre incubado tanto en atmósfera aerobia como anaerobia (BD Columbia Agar con 5% Sheep Blood, Becton Dickinson, Franklin Lakes, NY), a 37ºC. Se utilizó el sistema AnaeroGen Compact anaerobic system (Oxoid Ltd, Wide Road, Basingstoke, England) para la incubación en atmósfera anaerobia. La tinción de Gram de los hemocultivos reveló abundantes bacilos grampositivos; a las 18 horas de incubación, se observaron abundantes colonias de esos microorganismos en cultivo puro, solamente en agar sangre incubado en atmósfera anaerobia (Figura 1). La identificación se realizó mediante MALDI-TOF MS versión 9 (Bruker Biotyper, Billerica, MA) como *E. aldenen-*

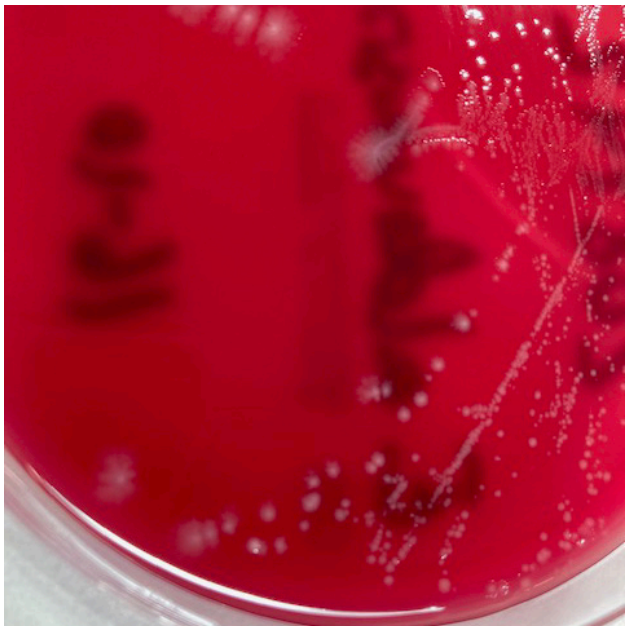

Figura 1 | **Aspecto de las colonias de *Enterocloster aldenensis* en cultivo puro a las 24 horas de incubación en agar sangre en atmósfera anaerobia.**

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sis (score 2.05). Además, el aislado fue enviado al Centro de Genómica e Investigacion Oncológica para secuenciación del gen 16S rRNA [4]. Se obtuvo un fragmento de 1416 pb con una similaridad del 99.35% con la secuencia del GenBank del aislamiento tipo *Clostridium aldenense* ATCC BAA-1318. La secuencia 16S se envió posteriormente al GenBank (número de acceso: PP234987).

El antibiograma se realizó mediante tiras de gradiente (E-test) en base a los criterios EUCAST de 2021 para microorganismos que no tienen puntos de corte [5]. Se obtuvieron las siguientes CMIs: benzylpenicilina (0.38 mg/L), piperacilina-tazobactam (0.75 mg/L), clindamicina (>256 mg/L), meropenem (0.094 mg/L), y metronidazol (0.023 mg/L). Tras 25 días de ingreso, en el que el paciente fue tratado durante 6 días con meropenem (1 g/8 h), el paciente fue dado de alta con mejoría de su situación, permaneciendo estable a los 6 meses de seguimiento.

Las infecciones debidas al género *Enterocloster* son extremadamente raras. En nuestro conocimiento, esta es la primera bacteriemia descrita en cultivo puro; recientemente se ha publicado una bacteriemia debida a *Enterocloster* pero de naturaleza polimicrobiana [3]. Dada su rareza, el conocimiento de su epidemiología y patogenia es escaso. De la descripción original, 4 aislamientos de *C. aldenense* fueron aislados de muestras intraabdominales, por lo que parece deducirse que este microorganismo forma parte de la microbiota intestinal [1]. En nuestro caso, la posible fuente de infección pudo ser también abdominal, puesto que el paciente había sido intervenido de una perforación colónica y durante este ingreso fue atendido por una eventración abdominal completa. La introducción de MALDI-TOF MS como herramienta diagnóstica ha supuesto un gran avance para la identificación bacteriana, en especial de los microorganismos anaerobios. Microorganismos que antes no se identificaban, ahora se pueden identificar de forma correcta mediante esta técnica. Este hecho está suponiendo la identificación de nuevos microorganismos, como el que presentamos, como causantes de infecciones graves.

En cuanto a la sensibilidad a antimicrobianos de *E. aldenensis,* Warren *et al.* La describieron frente a 13 aislamientos; en general, tanto la CMI_{50} como la CMI_{90} frente a los principales antimicrobianos anaerobicidas testados fue baja, excepto en piperacilina-tazobactam y clindamicina. Nuestro aislamiento fue sensible a todos los antibióticos testados, excepto a clindamicina (CMI >256 mg/L).

En conclusión, este es el primer caso de bacteriemia producida por *E. aldenensis*, aislado en cultivo puro, y confirmado por secuenciación del gen 16S rRNA, que indica que este patógeno puede ser responsable de infecciones graves. Este caso enfatiza la necesidad de realizar un diagnóstico correcto de todas las infecciones por anaerobios mediante las técnicas de que disponemos actualmente; además, sería recomendable realizar antibiograma a todo este tipo de microorganismos que causan infecciones graves para evaluar las tendencias de la posible aparición de resistencias

CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

FINANCIACIÓN

Los autores declaran que han recibido financiación para la realización de este estudio.

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