REVISTA ESPAÑOLA DE Quimioterapia

SPANISH JOURNAL OF CHEMOTHERAPY

ISSN: 0214-3429
Volumen 35
Número 2
Abril 2022
Páginas: 105-230

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)

Secretaría técnica
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
28040 Madrid
revista@seq.es
Disponible en Internet:
www.seq.es

Sociedad Española de Quimioterapia

Publicidad y Suscripciones
Sociedad Española de Quimioterapia
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
28040 Madrid

Atención al cliente
Teléfono 91 394 15 12
Correo electrónico
info@seq.es

Consulte nuestra página web
www.seq.es

Publicación que cumple los requisitos de soporte válido

ISSN
0214-3429

e-ISSN
1988-9518

Depósito Legal
M-32320-2012

Maquetación
Vic+DreamStudio

Impresión
España

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

REVISTA ESPAÑOLA DE
Quimioterapia

XYDALBA®, EL ÚNICO ANTIBIÓTICO QUE PERMITE TRATAR TODO EL CURSO DE LA INFECCIÓN* CON 1 SOLA DOSIS INTRAVENOSA EN 30 MINUTOS[1,2]

Xydalba®

*Indicado para el tratamiento de infecciones bacterianas agudas de piel y de los tejidos blandos de la piel en adultos.[1]

ANGELINI PHARMA

4329 - Febrero 2021

BIBLIOGRAFÍA:
1- Ficha técnica Xydalba
2- Centro de información online de medicamentos de la AEMPS (CIMA). Criterios de búsqueda: Principio activo (dalbavancina), cantidad de principios activos (1) y comercializado. Disponible en [último acceso febrero 2021]: https://cima.aemps.es/cima/publico/lista.html.

Sumario

REVISTA ESPAÑOLA DE Quimioterapia

Volumen 35
Número 2
Abril 2022

Sumario

REVISTA ESPAÑOLA DE Quimioterapia

Volumen 35
Número 2
Abril 2022

Creating Possible

Durante más de 30 años, en Gilead hemos conseguido avances que parecían imposibles, dirigidos a personas con enfermedades que amenazaban su vida. Somos una compañía biofarmacéutica puntera, con productos pioneros en sus áreas y con una, cada vez más, prometedora cartera de medicamentos en investigación.

Pero nuestro compromiso aún va más allá. Innovamos con el propósito de eliminar barreras y conseguir que las personas que más lo necesitan puedan tener acceso a los avances en el cuidado de la salud. Trabajamos para conseguir un mundo mejor y más saludable para todos.

GILEAD
Creating Possible

ES-GIL-2020-06-0007

Contents

REVISTA ESPAÑOLA DE Quimioterapia

Volume 35
Number 2
April 2022

Contents

REVISTA ESPAÑOLA DE Quimioterapia

Volume 35
Number 2
April 2022

VABOREM®
meropenem/vaborbactam

¿SOSPECHA DE CRE-KPC?
UNA NUEVA Y VALIOSA OPCIÓN PARA CRE.[1]

GRUPO MENARINI
www.menarini.es

▼ **Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.**

1. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther 2018;7:439–455.

Para un uso correcto ver Ficha Técnica:
www.menarini.es/fts/vaborem/

ESVAB21019 Jun'21

Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
doi:10.37201/req/149.2021

Booster or additional vaccination doses in patients vaccinated against COVID-19

Alejandra García-Botella[1]
Alberto García-Lledó[2]
Javier Gómez-Pavón[3]
Juan González del Castillo[4]
Teresa Hernández-Sampelayo[5]
Mari Cruz Martín-Delgado[6]
Francisco Javier Martín Sánchez[7]
Manuel Martínez-Sellés[8]
José María Molero García[9]
Santiago Moreno Guillén[10]
Fernando Rodríguez-Artalejo[11]
Julián Ruiz-Galiana[12]
Rafael Cantón[13]
Pilar De Lucas Ramos[14]
Emilio Bouza[15]

[1]General Surgery Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[2]Cardiology Service. Prince of Asturias Hospital. University of Alcalá. Madrid.
[3]Geriatrics Service. Central Hospital of the Red-Cross. Alfonso X el Sabio University. Madrid.
[4]Emergency Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[5]Pediatrics and ACES Service. Gregorio Marañón General University Hospital, Complutense University. Madrid.
[6]Intensive Medicine Service. Torrejón University Hospital. Francisco de Vitoria University. Madrid.
[7]Geriatrics Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[8]Cardiology Service. Gregorio Marañón General University Hospital, European University. Madrid.
[9]Family Medicine. Infectious diseases. Madrid.
[10]Infectious Diseases Service. Ramón y Cajal Hospital. University of Alcalá de Henares. Madrid.
[11]Department of Public Health. Autonomous University. Madrid.
[12]Internal Medicine Service. Ruber International Hospital. Madrid.
[13]Microbiology Service. Ramón y Cajal Hospital and Ramón y Cajal Institute for Health Research (IRYCIS). Spanish Network for Research in Infectious Pathology (REIPI). Madrid.
[14]Emeritus. Pneumology Service. Gregorio Marañón General University Hospital, Complutense University. Madrid
[15]Clinical Emeritus, Community of Madrid. Clinical Microbiology and Infectious Diseases Service of the Gregorio Marañón General University Hospital, Complutense University. CIBERES. Cyber of Respiratory Diseases. Madrid

Article history
Received: 5 November 2021; Accepted: 10 November 2021; Published: 15 November 2021

ABSTRACT

Several health organizations, mainly in Western countries, have recently authorized the use of a booster dose of the COVID-19 vaccine for patients previously vaccinated with mRNA vaccines, with criteria that do not always coincide.

The COVID Scientific Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has received and asked several questions about this situation, to which the group has tried to give answers, after deliberation and consensus.

The efficacy of the vaccines administered so far is beyond doubt and they have managed to reduce, fundamentally, the severe forms of the disease. The duration of this protection is not well known, is different in different individuals and for different variants of the virus and is not easily predictable with laboratory tests.

Data on the real impact of a supplementary or "booster" dose in the scientific literature are scarce for the moment and its application in large populations such as those in the state of Israel may be associated with a decrease in the risk of new and severe episodes in the short observation period available.

We also lack sufficient data on the safety and potential adverse effects of these supplementary doses and we do not know the ideal time to administer them in different situations.

In this state of affairs, it seems prudent to administer supplemental doses to those exposed to a higher risk, such as immunocompromised individuals and the elderly. On the other hand, we consider that this is not the time to accelerate, on the spur of the moment, a massive administration of a third dose to other population groups that are less exposed and at lower risk, without waiting for adequate scientific information, which will undoubtedly arrive gradually.

We do not believe that this position is incompatible with the practical and ethical warnings made by the World Health Organization in this respect.

Keywords: COVID-19, SARS-CoV2, vaccines, additional doses, third dose, booster

Dosis vacunales de recuerdo o adicionales en pacientes vacunados frente a COVID-19

RESUMEN

Varias organizaciones sanitarias, fundamentalmente de países occidentales, han autorizado recientemente el uso de una dosis de refuerzo de la vacuna frente al COVID-19 para pacientes previamente vacunados con vacunas mRNA, con criterios no siempre coincidentes.

El Comité Científico de COVID, del Ilustre Colegio de Médicos de Madrid (ICOMEM) ha recibido y se ha formulado diversas preguntas sobre esta situación, a la que el grupo ha tratado de dar respuestas, tras deliberación y consenso.

La eficacia de las vacunas administradas hasta el momento está fuera de toda duda y han logrado disminuir, funda-

Correspondence:
Emilio Bouza Servicio de Microbiología Clínica y Enfermedades Infecciosas del Hospital General Universitario Gregorio Marañón, Universidad Complutense. CIBERES. Ciber de Enfermedades Respiratorias. Madrid
E-mail: emilio.bouza@gmail.com

All authors belong to the Scientific Committee on COVID-19 of the Madrid College of Physicians (ICOMEM).

mentalmente, las formas graves de enfermedad. La duración de esa protección no se conoce bien, es diferente en distintos individuos y para distintas variantes del virus y no es fácilmente predecible con pruebas de laboratorio.

Los datos sobre el impacto real de una dosis complementaria o "booster" en la literatura científica son escasos por el momento y su aplicación en grandes poblaciones como las del estado de Israel pueden asociarse a una disminución del riesgo de nuevos episodios y episodios graves en el corto periodo de observación disponible.

Carecemos también de datos suficientes sobre la seguridad y potenciales efectos adversos de estas dosis complementarias e ignoramos el momento idóneo de administrarlas en distintas situaciones.

En este estado de cosas, parece prudente administrar dosis complementarias a aquellos expuestos a un mayor riesgo, como pueden ser los individuos inmunodeprimidos y las personas mayores. Por el contrario, consideramos que no es este el momento de acelerar improvisadamente una administración masiva de una tercera dosis a otros grupos de población menos expuesta y de menor riesgo, sin esperar la adecuada información científica, que sin duda irá llegando paulatinamente.

No creemos que esta posición, sea incompatible con las advertencias prácticas y éticas que realiza la Organización Mundial de la Salud a este respecto.

Palabras clave: COVID-19, SARS-CoV2, vacunas, dosis adicionales, tercera dosis, booster

INTRODUCTION

Several health organizations, mainly in Western countries, have recently authorized the use of a booster dose of COVID-19 vaccine for previously vaccinated patients, with criteria that do not always coincide. In this regard, the European Centre for Disease Prevention and Control (ECDC) on September 1st, 2021 [1], stresses the importance of distinguishing between booster doses and additional doses. The former (booster doses) are those administered to persons with normal immune systems, who have responded adequately to vaccination, to reestablish protection after it has decreased, and the latter (additional doses) refer to those administered to persons with weakened immune systems, who did not respond adequately to vaccination. For the sake of simplicity we will refer to both as complementary doses.

Spain, like other countries in its environment and situation, has authorized the use of complementary doses for certain segments of the population.

In contrast to this situation is the proposal of the World Health Organization (WHO), which advocates vaccinating millions of people around the world who have not yet had the option of receiving any dose, before proceeding to the massive use of complementary doses in economically more affluent countries.

The COVID Scientific Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has received and asked several questions about this situation, to which the group has tried to give answers, after deliberation and consensus.

The following pages contain not only the scientific evidence that we have managed to collect on the questions received immediately, but also the opinion of the group where evidence is scarce or non-existent at this time. It should be noted that the vast majority of the information available at this time is that of the Pfizer mRNA vaccine.

1.- IS THERE, AT THIS TIME, A LOSS IN THE DURATION OF PROTECTION MORE THAN SIX MONTHS AFTER VACCINATION?

The efficacy of the different vaccines has been demonstrated both in clinical trials and in post-vaccination observational studies. However, from the beginning there has been uncertainty about the duration of protection, particularly in those subjects in whom an adequate antibody response to the vaccines was not detected. In relation to this, the need for a supplementary dose has been raised, making a speculative balance between risks and benefits, in some population groups. Months after the start of vaccination in some countries, data are becoming available that attempt to answer these open questions.

In the 5-month blinded follow-up phase of trials conducted with both the mRNA-1273 (Moderna) and BNT162bm (Pfizer) vaccines, data have been reported showing an overall clinical effectiveness of over 95% for severe disease and around 65% for asymptomatic disease. Efficacy is lower for the 65-75 age group [2]. These data extend those reported in the clinical trial with the mRNA Pfizer's vaccine in which follow-up was limited to two months [3].

Already in real life, studies in large populations confirm the efficacy data found in clinical trials [4,5]. However, as observation time progresses, there are some differences related to age groups and in some cases to disease progression.

In the Glatman-Freedman study [4], carried out in Israel, efficacy data were obtained at 14, 21 and 28 days post-vaccination follow-up. The infection rates found were very low, with an estimated efficacy of over 95% for overall infection, symptomatic infection, hospitalization and death. Butt et al., in the United States, report an incidence of COVID at 3 months, in vaccinated population, of 0.1% compared to 6% in the unvaccinated population [5]. In Qatar, a study was conducted to determine the severity of disease in vaccinated versus unvaccinated patients, including 456 cases in each group, finding a marked reduction in severe disease in vaccinated patients, 10.1% vs. 46% [5]. Age is the main risk factor for severity which spikes in both groups above the age of 60 years.

The concern arises when the incidence is broken down by months post-vaccination. In a study published in July 2021 [6] 3 cohorts were analyzed corresponding to those vaccinated with mRNA-1273, with BNT162b2,3 and those not vaccinated, with a follow-up of 6 months. With both cohorts there

was a drop in disease prevention, which was 86% with mRNA-1273 and 76% with BNT162b2. In the analysis performed by months, the figures for disease prevention drop to 76% and 52% respectively, but the effectiveness in reducing hospitalization and severity is maintained. Although speculative, the authors point out that both the loss of effectiveness and the difference between vaccines could be related to the different variants, predominantly alpha at the beginning and delta in July. These results are similar to those published in October 2021 in Lancet in which the effectiveness of the BNT162b2 vaccine above the 5th month is 53% for delta variant infection and 67% for other variants, but remaining at around 90% for hospitalizations [7].

The loss of effectiveness, especially in the elderly, could be due to the different immune response. In a cohort study comparing the elderly and health care workers, both with a complete vaccination schedule, antibodies measured six months after immunization were significantly lower in the elderly than in the health care workers [8]. The possible impact of previous infection on the occurrence of disease in vaccinated patients has also been analyzed. A large retrospective study carried out in Israel comparing 3 cohorts (vaccinated with complete regimen, unvaccinated infected and infected and vaccinated) concludes that natural immunity confers greater duration and protection against reinfection by the delta variant so that those vaccinated and not previously infected have a 5.96-fold increased risk (95% CI, 4.85 to 7.33) of reinfection, compared with the two cohorts previously infected and even greater in the group over 60 years of age [9].

Finally, the results obtained with the application of a complementary dose of vaccine have recently been published, which would increase the effectiveness to 90%, although the results are only at 3 weeks [10].

In summary, with up to 6 months of follow-up after vaccination, although good protection against infection and complicated disease continues to be observed, data have emerged that point to loss of vaccine efficacy over time, with some discordance in relation to severity. Although with reservations, due to the scarce evidence available, and the need to replicate results, the need for a vaccine booster is being debated, at least in the most vulnerable population.

2.- ARE THERE RELIABLE LABORATORY MARKERS TO DETERMINE THE RISK OF INFECTION OR REINFECTION?

At present, there is no agreement on which laboratory markers can ensure or predict the risk that a person who has been vaccinated against SARS-CoV-2 without having previously had COVID-19 will develop a SARS-CoV-2 infection. Nor is it possible to evaluate the risk of reinfection by SARS-CoV-2 in vaccinated individuals who have had COVID-19 prior to vaccination. In the latter, the immune response is higher since vaccination would reactivate the memory B cells, stimulating the humoral response and could generate greater protection [11].

IgG antibodies to N antigen (nucleocapsid) or S antigen (spicule) can now be routinely measured. Both can be positive in persons who have been naturally infected, whereas in those who have been vaccinated and have not been infected, only IgG antibodies to the S antigen will be positive [12]. The measurement of neutralizing antibodies or the cellular response to SARS-CoV-2 is not currently standard practice and is performed in research work or specific series of individuals. However, tests are being introduced that detect IgG against the RBD (Receptor Binding Domain) of the spike and whose result, due to its good correlation, could be used as a surrogate value for neutralizing antibodies determined with cell culture reference techniques [13].

In the analysis of gap infections in individuals vaccinated with both doses of Pfizer's vaccine and who had IgG-anti S antibody data, gap infections occurred more severely in those with lower antibody rates with no significant difference [14]. In addition, antibody levels were measured with two different techniques depending on the patient, and no common pattern could be observed when comparing the values of both techniques. In many of the patients, the values exceeded the cut-off values for positivity established by the manufacturer, resembling those that may be present in vaccinated individuals without subsequent infection. Cases of infection have also been reported in vaccinated individuals with adequate neutralizing antibody titers [15]. In cases of reinfection, what has been demonstrated is a rapid reduction in neutralizing antibody titers prior to reinfection. [16].

Although at present, at least in Spain, a specific type of variant (Delta variant) dominates, in the future it will be important to clarify not only which are the antibody titers that determine the specific level of protection of the individual but also whether these breakthrough infections are more related to the type of variant than to the quality of the previous immune response. What is easier to affirm, and on which there is unanimous agreement, is that the populations of immunosuppressed individuals, patients with immunosuppressive treatments, older and with worse immune response are those with the highest risk of reinfection or gap infection and in whom it will be necessary to establish priority plans for the administration of additional doses of vaccine or with vaccines directed at new variants.

3.- WHAT IS THE POSITION OF THE U.S. FDA AND CDC ON THE ADMINISTRATION OF ADDITIONAL AND BOOSTER DOSES OF VACCINE?

Following an initial FDA proposal, on September 24, 2021, the Director of the CDC approved and adopted the recommendations of the ACIP (Advisory Committee on Immunization Practices) for the administration of booster doses of the Pfizer-BioNTech Covid-19 vaccine in persons selected by age, underlying disease or population considered at high risk of exposure and infection by COVID-19 due to their professional or institutional activity [17].

It will be administered to persons who meet the defined recommendations and who have previously received the complete vaccination with Pfizer-BioNTech Covid-19 vaccine. The additional booster dose will be with the same vaccine and at least 6 months after completion of the primary vaccination.

Recommendations to administer supplemental doses in the U.S. are as follows:

- Persons 65 years of age or older, and/or residents of long-stay facilities.

- Persons aged 50-64 years with underlying medical conditions.

- Persons aged 18-49 years with underlying medical pathology, in whom the risk-benefit of receiving the booster dose will be assessed on an individual basis.

- Persons aged 18-64 years with high risk of exposure and transmission of COVID-19, due to work or institutional circumstances may receive the "booster", individually assessing their risk-benefit of being vaccinated.

The CDC justifies the booster dose in the chosen groups because they were the first to be vaccinated at the beginning of the vaccination campaigns and can now benefit from additional protection. Given that the Delta strain is still circulating in the United States, the booster would help the most vulnerable population by protecting them against severe COVID-19 and its complications, which are more frequent in these groups. The CDC is committed to continuing to monitor the safety and effectiveness of the COVID-19 vaccines so that new booster recommendations can be added in the coming weeks for other population groups and for those who have previously received the other vaccines.

CDC Director Dr. Walensky acknowledges the great challenge of making high-impact decisions when analyzing very complex situations with insufficient and sometimes poor-quality data to make very specific recommendations. In a pandemic, the greatest benefit is obtained if action is taken in anticipation of its evolution despite the uncertainty with which we have to work.

These are the first steps in the indications of the "booster", which will be completed in the near future. It is important not to forget and to insist on the need to achieve greater vaccination coverage with complete primary vaccination in the population not yet vaccinated, both in the United States and in the rest of the world.

4.- WHAT IS THE EUROPEAN POSITION, PARTICULARLY THAT OF THE ECDC?

The ECDC, bearing in mind that the primary objective of the vaccination strategy is to prevent severe cases of COVID19, was in favor of considering the administration of a supplemental vaccine dose, as an extension of the vaccination series, to persons who may experience a limited response to the primary COVID-19 vaccination series, such as some categories of immunocompromised individuals (e.g., solid organ transplant recipients) [18]. In addition, they advised considering, as a precautionary measure, the possibility of providing a booster dose for the elderly and frail, particularly those living in closed environments (socio-health centers) [18]. Regarding the need for the administration of booster doses of vaccines to fully vaccinated individuals in the general population, they considered that this was not an urgent decision, as the evidence available at this time regarding "real world" vaccine effectiveness and duration of protection shows that all licensed vaccines in the EU are highly protective against COVID-19-related hospitalization, severe illness and death. In this situation, they noted that the priority should be to vaccinate all those who have not yet completed their recommended vaccination course [18].

In a statement dated September 2, 2021 [1], the EMA aligned itself with the positioning of the ECDC technical report. On October 4, 2021, the EMA's Committee for Medicinal Products for Human Use (CHMP), following an accelerated evaluation of the results of studies on the efficacy of administering additional doses of mRNA vaccines [19,20], both in immunocompromised adults and in vaccinated individuals with healthy immune systems, reached the following conclusions:

Administer an additional dose of the COVID-19 vaccines Comirnaty (BioNTech / Pfizer) and Spikevax (Moderna) to people with severely weakened immune systems at least 28 days after the second dose. The recommendation comes after studies showed that an additional dose of these vaccines increased the ability to produce antibodies against the virus that causes COVID-19 in organ transplant patients with weakened immune systems.

a) Consider a booster dose of COVID-19 Comirnaty vaccine (BioNTech / Pfizer) at least 6 months after the second dose for persons 18 years of age or older with normal immune systems. The data evaluated show an increase in antibody levels when a booster dose is administered approximately 6 months after the second dose in persons aged 18 to 55 years.

b) At the national level, public health agencies in EU states may issue official recommendations on the use of booster doses, taking into account emerging efficacy data and limited safety data.

Currently, the Committee for Medicinal Products for Human Use is evaluating data to support a booster dose of Spikevax (Moderna) [20].

5.- WHAT DOES THE WHO RECOMMEND AT THIS TIME REGARDING THE ADMINISTRATION OF BOOSTER DOSES TO PEOPLE WHO HAVE ALREADY BEEN VACCINATED?

In a press release dated August 10, 2021 [21], WHO stated that "In the context of current global vaccine supply constraints, the administration of booster doses will exacerbate inequities by increasing demand and consuming a scarce supply, while priority populations in some countries, or subnational settings, have not yet received a primary vaccination series. For the time being, the goal remains to increase global vacci-

nation coverage with the primary series (one or two doses for current vaccines)."

Furthermore, WHO adds that "the introduction of supplementary doses should be strongly evidence-based and targeted to the population groups most in need. The rationale for booster doses should be guided by evidence of decreased vaccine efficacy, in particular decreased protection against severe disease in the general population or in high-risk populations, or due to a coronavirus variant of concern. To date, evidence remains limited and inconclusive on the widespread need for booster doses following a primary vaccination series. WHO is carefully monitoring the situation and will continue to work closely with countries to obtain the necessary data for policy recommendations.

On September 11, 2021, Katherine O'Brien, director of WHO's Department of Immunization, Vaccines and Biological Medicines, ratifies this same position in a statement on the Organization's own website [22].

Finally, Mike Ryan, Executive Director of WHO's Health Emergencies Programme, during a live question and answer session broadcast on September 22, 2021 on the Organization's social media channels [23] said what WHO is advocating is that booster doses in the general population, who have had broad access to vaccines and have already been vaccinated, are not the best option at this time. However, Ryan indicated that WHO is not against giving a third dose to people who may have significant benefit, such as the elderly, the medically vulnerable, and anyone who needs an immune system booster after a full regimen of COVID-19 vaccines. Dr. Ryan understands that this is compatible with giving the primary vaccine series to everyone in the world who needs it because there is enough vaccine.

6.- WHAT IS THE RECOMMENDATION AND EXPECTED EFFICACY OF COMPLEMENTARY VACCINE DOSES IN IMMUNOSUPPRESSED PATIENTS?

It seems to be demonstrated that, in general, COVID-19 is more severe, more prolonged, with a greater possibility of maintaining a high viral load for a longer period of time and, therefore, with a greater capacity for transmission in the immunocompromised population. [24-28].

Likewise, the humoral response to vaccines and in particular to those available against COVID-19, is lower in immunocompromised patients, both in primary deficiencies and in those associated with infectious and autoimmune diseases. [14, 29-31], as well as in oncology patients and notably more evident in certain tumor and treatment subgroups. [14, 29, 32, 33].

The "booster" effect of the antibody level response with the second dose of the vaccine and with vaccination after the infection has passed is also certain.

Due to this foreseeable immunogenic potentiation of additional doses to the standard vaccination, the CDC and then other global health agencies were ahead of the evidence and recommended in the summer of 2021 the third dose for the population that had had a worse response to the vaccine (immunosuppressed) and have recently ratified and have proposed the extension to other risk groups and even to the general population from the 6th month after vaccination.

There were not enough studies of extra doses when the first recommendations were made and we still have little evidence of increased efficacy in the real world, given the very short time elapsed since the beginning of the administration of "third doses" and the obtaining of evolutionary data that can be analyzed beyond the titration of antibodies.

It occurs in both the general population [10], as in the aforementioned immunosuppressed groups.

Solid organ transplant recipients. The first information demonstrating the potentiating effect of the third dose comes from series of patients with solid organ transplants [34-36] and whose review concludes that:

- The 3rd dose of mRNA vaccine against COVID-19 in solid organ transplant recipients (with a high percentage of renal transplants), improves immunogenicity, reaching neutralizing antibody titers in half of the patients who did not have them after the second dose.

- In some studies the levels achieved would correspond to neutralizing capacity against the virus in in vitro studies.

- The results obtained on the activation of cellular immunity do not allow a correlation with the clinical efficacy of this response.

- The existing series do not report cases of COVID-19 after the 3rd dose, but the follow-up is too short to be able to verify clinical efficacy.

- In solid organ transplant recipients who receive a 3rd dose of vaccine, there are no serious adverse side effects.

- Objective signs of organ rejection after the 3rd dose have only been reported in one heart transplant recipient, with no organ failure in the follow-up up to the date of publication.

- The presence of neutralizing antibodies, even at low doses, after the 2nd dose, predicts an enhanced response after the 3rd dose.

- The more immunosuppressive drugs, the less response from the 3rd dose.

- Corticosteroids, tacrolimus, mycophenolate and belatacept, decrease the response to the 3rd dose and more in combination.

- Slightly more than half of solid organ transplanted patients do not seroconvert after the 3rd dose of vaccine.

Renal transplant and dialysis patients. France authorized in April 2021, the additional doses for renal patients (transplanted or on dialysis), their series were brought forward to add knowledge of the response in this group [37-39] and their conclusions are:

- The third dose in renal transplant patients and in dia-

lyzed patients, increases the immunogenic response, although more than 50% of complete vaccine non-responders remain non-seroconverted.

- The higher the immunosuppressive treatment load, the lower the humoral response. In dialyzed patients it is significant in those receiving immunosuppressants for myeloma or amyloidosis.

- There are no serious adverse side effects.

Other cohorts of patients with immunosuppression and booster doses. There are no analyzable series, for the moment, of 3rd dose or additional dose to the standard vaccine in patients under immunosuppressive treatment of patients with autoimmune diseases or other types of oncologic patients (solid organ or hematologic) different to those already mentioned. Neither in patients under immunotherapy, a group in which the safety of the vaccine was especially valued due to initial suspicions of the possibility of potentiation of adverse effects.

Only the sum of particular actions in this group are available without alarm bells ringing in the updated literature [40, 41].

7.- WHAT IS KNOWN ABOUT THE INDICATION AND EFFICACY OF BOOSTER DOSES OF NON-mRNA VACCINES?

Existing information on the efficacy of additional doses of vaccines other than mRNA vaccines is still very scarce. The available data refer mainly to the Johnson & Johnson vaccine. Two studies, not yet published, have been carried out with this vaccine. The first phase 3 study (ENSEMBLE-2) is a double-blind, placebo-controlled study evaluating the safety and efficacy of a two-dose regimen of the vaccine administered at an interval of 56 days to adults over 18 years of age at high risk of severe COVID-19 [42, 43]. After a median follow-up of 36 days, a second dose was shown to achieve 100% (CI, 33%-100%) protection against severe/critical COVID-19 at least 14 days after the final vaccination, 76% (55%-88%) against symptomatic COVID-19 globally, and 94% (58%-100%) against symptomatic COVID-19 in the United States. The second dose of vaccine was generally well tolerated [44]. In the second study, the second dose was administered 6 months after the first dose. In this case, a 9-fold increase in antibody levels was observed at 1 week after administration and increased up to 12-fold at 4 weeks. By comparison, when the second dose was administered two months after the first dose, antibody levels had risen 4 to 6-fold [45]. The data are not yet published and approval for the administration of the booster dose of this vaccine has not yet been received.

8.- IS THERE REALLY A CONFLICT IN THE USE OF BOOSTER DOSES OF VACCINES IN HIGHLY DEVELOPED NATIONS VERSUS LESS FAVORED ONES?

In view of the dilemma that could arise regarding the administration of a supplementary dose to fully vaccinated patients in certain countries versus achieving a complete vaccination schedule in the unvaccinated population worldwide, a certain debate has been established [46]. Most institutional positions recommend the administration of the booster dose in certain vulnerable populations (immunocompromised, elderly, nursing homes) but not to the entire population in a comprehensive manner, for which there would not be as much evidence or urgency to do so. Regardless of the relevance of a booster campaign, this situation may generate an ethical debate, balancing the national and international responsibilities of the states [47]. The WHO already states that this situation may increase the inequality of access to vaccines in the different countries of the world, where there are still countries such as the African continent where the complete vaccination rate is around 3%. Thus, although there are cosmopolitan positions that consider a global strategy to defeat the pandemic (reduction of transmission and possibility of new variants) to be pragmatic, the reality is that countries have adopted national policy strategies in the absence of a consensus. This nationalism as a strategy would be based on the investment of local resources and public funds in vaccine research and the concept of protecting their population as much as possible. The question is whether the booster dose in certain countries is really an opportunity cost for the poorest countries or whether there are other barriers beyond vaccine shortages that prevent vaccines from reaching the unvaccinated population [46]. Thus, increasing global access to vaccination should be a priority for all states, while seeking to improve the evidence of the effectiveness of a booster dose in certain populations.

Perhaps it is not a matter of choosing between one option or another, but rather of seeking alternatives that favor global vaccination aimed at solving certain issues such as the loss of the cold chain, the possibility of heterologous vaccination or local production together with compliance with the established distribution agreements through programs such as COVAX, which have not met their expectations at present [48]. The objective would be to reduce inequity in the poorest countries, while maintaining the national commitment of the richest countries in the development of vaccines and promoting their distribution in an international framework.

9.- WHAT IS THE FUTURE OF VACCINATION AS A COVID-19 PREVENTION TOOL? WILL PERIODIC VACCINATION WITH THE COVID VACCINE BE NECESSARY?

The need for repeat supplemental doses of the COVID vaccine depends on whether the pandemic evolves into an endemic form of infection, such as influenza. This is the future scenario that is considered most likely, both because of the evolution of previous pandemics and because of the existence of many conditions that make it easier for the virus not to be eradicated. Even with the best progress in vaccination, it seems likely that reservoirs of SARS-CoV-2 may remain in both unvaccinated populations and animals, as is the case with other coronaviruses. The ability of SARS-CoV-2 to mutate makes it possible for more

transmissible and vaccine-resistant variants to emerge, making it possible that a multivalent vaccine covering several SARS-CoV-2 strains may be required in the future. The possibility of an endemic infection will also depend on a possible waning of acquired immunity against the virus and its variants, something we will only know in the long term. If this is the case, the time when epidemic peaks are expected to occur will coincide with the influenza season, as the cold conditions less time outdoors and more personal contact. This makes it possible for both vaccination campaigns to coincide [49-51].

10.- WHAT IS THE POSITION OF THE COVID SCIENTIFIC COMMITTEE OF ICOMEM ON THE ISSUE OF THE ADMINISTRATION OF SUPPLEMENTARY DOSES OF VACCINES TO THE SPANISH POPULATION?

The efficacy of the vaccines administered to date is beyond doubt and they have managed to reduce, fundamentally, severe forms of disease, those requiring hospital admission, ICU admissions and deaths due to COVID-19. However, the vaccines administered to date do not totally prevent the acquisition of viral infection and transmission to third parties. The duration of this protection is not well known and it happens to be different in different individuals and for different variants of the virus. In any case, at present, protection cannot be firmly deduced from tests such as the determination of antibody titers or other immunological determinations.

There are breakthrough infections in vaccinees and reinfections in patients who have already had a primary episode of COVID, some of them severe and fatal.

Data on the real impact of a complementary or "booster" dose are scarce in the scientific literature. An additional dose may induce the appearance of antibodies for example in up to 50% of solid organ transplant patients who had not responded adequately to previous vaccination and booster doses in large populations such as those in the state of Israel may be associated with a decreased risk of new and severe episodes in the short observation period available.

On the other hand, data on the safety and potential adverse effects in vaccinated individuals when exposed to a new dose are limited and even less on the ideal timing of administration in different situations.

In this state of affairs, it seems prudent to administer supplementary doses to those exposed to a higher risk, such as immunocompromised individuals and the elderly, particularly among those most at risk because they live in health care facilities.

On the contrary, we consider that this is not the time to improvise a massive administration of a third dose to other population groups less exposed and at lower risk, without waiting for adequate scientific information, which will undoubtedly arrive gradually.

We do not believe that this position is incompatible with the practical and ethical warnings issued by the World Health Organization. The arrival of vaccines in the world with a low prevalence of vaccinated people should be compatible with the additional doses needed in countries of the economically richer world. It should not be forgotten that the arrival of vaccines to millions of disadvantaged human beings who have not received them so far depends not only on the will or generosity of the nations that possess them. We are aware that there are political, economic, logistical and technical factors that can make the best will to help and solidarity of some human beings with others fail.

CONCLUSIONS

1.- More than six months after the application of the first vaccines against COVID, a high level of protection is maintained, particularly against severe forms of the disease.

2.- Vaccine failures are detected, however, particularly in patients with severe immunosuppression such as solid organ transplant recipients.

3.- Current routine laboratory markers do not allow definitive detection of the most exposed vaccinated population.

4.- Both North American and European health authorities admit, in the absence of very solid data on their efficacy, the administration of complementary doses for the most vulnerable population, the definition of these populations being somewhat diffuse and rapidly changing.

5.- Third doses are currently approved or in the process of being approved for at-risk populations, including those selected on the simple criterion of being over a certain age.

6.- The WHO, while not frankly opposing this trend, points to the need to vaccinate first those populations of the world that have not yet had access to the vaccine on a massive scale.

7.- There are very few studies that evaluate the potential adverse effects of receiving a complementary dose of vaccine in large segments of the population, but some health authorities point to the need to "go ahead" of the pandemic and increase, accepting the uncertainty, the degree of immunization of the population.

9.- This Scientific Committee of COVID, of ICOMEM, supports the attitude of administering a third dose (complementary dose) to particularly vulnerable population groups but wishes to express the necessary caution when extending this recommendation indiscriminately to large population groups until more studies on both the efficacy and safety of this medical practice are available.

10.- We consider that getting the necessary vaccines to the world that needs them is not only a decision of solidarity, but that it runs up against logistical and political problems that cannot always be solved from a purely technical point of view.

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. European Centers for Disease Control. ECDC and EMA highlight considerations for additional and booster doses of COVID-19 vaccines. [Press release]. European Medicines Agency (EMA); (Assessed 27 sep 2021). Disponible en: https://wwwemaeuropaeu/en/news/ecdc-ema-highlight-considerations-additional-booster-doses-covid-19-vaccines.
2. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021. doi: 10.1056/NEJMoa2113017
3. Thomas SJ, Moreira E D Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021. doi: 10.1056/NEJMoa2110345
4. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, Keinan-Boker L. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021;72:103574. doi: 10.1016/j.ebiom.2021.103574 PMC8445746
5. Butt AA, Nafady-Hego H, Chemaitelly H, Abou-Samra AB, Khal AA, Coyle PV, et al. Outcomes Among Patients with Breakthrough SARS-CoV-2 Infection After Vaccination. Int J Infect Dis. 2021;110:353-8. doi:10.1016/j.ijid.2021.08.008 PMC8349447
6. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv. 2021. Aug 9;2021.08.06.21261707. doi: 10.1101/2021.08.06.21261707
7. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021. Oct 16;398(10309):1407-1416. doi: 10.1016/S0140-6736(21)02183-8.
8. Tober-Lau P, Schwarz T, Vanshylla K, Hillus D, Gruell H, EICOV/COVIM Study Group. Long-term immunogenicity of BNT162b2 vaccination in the elderly and in younger health care workers. Lancet Respir Med. 2021 Nov;9(11):e104-e105. doi: 10.1016/S2213-2600(21)00456-2..
9. Gazit S, Shlezinger R, Perez G, Lotan R, Peretz A, Ben-Tov A, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. . medRxiv 2021. doi: 10.1101/2021.08.24.21262415.
10. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021 Oct 7;385(15):1393-1400. doi: 10.1056/NEJMoa2114255
11. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling MJ, et al. Evolution of antibody responses up to 13 months after SARS-CoV-2 infection and risk of reinfection. EBioMedicine 2021; 71:103561 doi: 10.1016/j.ebiom.2021.103561.
12. Altawalah H. Antibody Responses to Natural SARS-CoV-2 Infection or after COVID-19 Vaccination. Vaccines (Basel). 2021;9(8). doi: 10.3390/vaccines9080910 PMC8402626
13. Anonimous. Recommendations for Prevention and Control of Influenza in Children, 2020-2021. Pediatrics. 2020. Oct;146(4):e2020024588. doi: 10.1542/peds.2020-024588
14. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021. Nov;27(11):1652-1657. doi:10.1016/j.cmi.2021.06.036
15. Hacisuleyman E, Hale C, Saito Y, Blachere NE, Bergh M, Conlon EG, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. N Engl J Med. 2021. Jun 10;384(23):2212-2218. doi: 10.1056/NEJMoa2105000
16. Vetter P, Cordey S, Schibler M, Vieux L, Despres L, Laubscher F, et al. Clinical, virologic and immunologic features of a mild case of SARS-CoV-2 reinfection. Clin Microbiol Infect. 2021;27(5):791.e1-4. doi: 10.1016/j.cmi.2021.02.010 PMC7896115
17. Anonimous. COVID-19 vaccines: no time for complacency. Lancet. 2020;396(10263):1607. doi: 10.1016/s0140-6736(20)32472-7
18. European Centre for Disease Prevention and Control. Interim public health considerations for the provision of additional COVID-19 vaccine doses, 1 September 2021. ECDC: Stockholm. [Assessed 27 sep 2021]. Available at: https://wwwecdceuropaeu/en/publications-data/covid-19-public-health-considerations-additional-vaccine-doses.
19. Agency EM. EMA evaluating data on booster dose of COVID-19 vaccine Spikevax (Assessed 27 sep 2021). Available at: https://wwwemaeuropaeu/en/news/ema-evaluating-data-booster-dose-covid-19-vaccine-spikevax..
20. Agency EM. EMA evaluating data on booster dose of COVID-19 vaccine Comirnaty [Press release]. (Assessed 27 sep 2021). Available at: https://wwwemaeuropaeu/en/news/ema-evaluating-data-booster-dose-covid-19-vaccine-comirnaty.
21. World Health Organization. Interim statement on COVID-19 vaccine booster doses. 2021. Available at: https://wwwwhoint/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses.
22. World Health Organization. Episode #53 - COVID-19: Booster Shots. Available at: https://wwwwhoint/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5/episode-53---covid-19-booster-shots?gclid=Cj0KCQjwkbuKBhDRARIsAALysV4nlk7tk_o96J1wr1U807jp3bZkYE61KdRbEg2jXTVR0RNTK0UREpgaAnHSEALw_wcB.

23. World Health Organization. Questions and Answers on Covid-19. 2021. Available at: https://wwwyoutubecom/watch?v=IN1BK4u3hio.
24. Venkatesulu BP, Chandrasekar VT, Girdhar P, Advani P, Sharma A, Elumalai T, et al. A systematic review and meta-analysis of cancer patients affected by a novel coronavirus. medRxiv. 2020 May 29;2020.05.27.20115303. doi: 10.1101/2020.05.27.20115303
25. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol. 2020;6(7):1108-10. doi: 10.1001/jamaoncol.2020.0980 PMC7097836
26. Wang Q, Berger NA, Xu R. Analyses of Risk, Racial Disparity, and Outcomes Among US Patients With Cancer and COVID-19 Infection. JAMA Oncol. 2021;7(2):220-7. doi: 10.1001/jamaoncol.2020.6178 PMC7729584
27. Berghoff AS, Gansterer M, Bathke AC, Trutschnig W, Hungerländer P, Berger JM, et al. SARS-CoV-2 Testing in Patients With Cancer Treated at a Tertiary Care Hospital During the COVID-19 Pandemic. J Clin Oncol. 2020;38(30):3547-54. doi: 10.1200/jco.20.01442 PMC7571795
28. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7. doi: 10.1016/s1470-2045(20)30096-6 PMC7159000
29. Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States. Clin Infect Dis. 2021. doi: 10.1093/cid/ciab687 PMC8436392
30. Thakkar A, Gonzalez-Lugo JD, Goradia N, Gali R, Shapiro LC, Pradhan K, et al. Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell. 2021;39(8):1081-90.e2. doi: 10.1016/j.ccell.2021.06.002 PMC8179248
31. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021;22(6):765-78. doi: 10.1016/s1470-2045(21)00213-8 PMC8078907
32. Bird S, Panopoulou A, Shea RL, Tsui M, Saso R, Sud A, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. Lancet Haematol. 2021;8(6):e389-e92. doi: 10.1016/s2352-3026(21)00110-1
33. Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, et al. Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose. Blood. 2021. doi: 10.1182/blood.2021011904
34. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021 Aug 12;385(7):661-662. doi: 10.1056/NEJMc2108861.
35. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med. 2021 Sep;174(9):1330-1332. doi: 10.7326/L21-0282.
36. Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021 Sep 23;385(13):1244-1246. doi: 10.1056/NEJMc2111462
37. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. JAMA. 2021 Jul 23;326(11):1063-1065. doi: 10.1001/jama.2021.12339
38. Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, et al. SARS-CoV-2 Antibody Response After a Third Dose of the BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. Am J Kidney Dis. 2021 Sep 8;S0272-6386(21)00833-7. doi: 10.1053/j.ajkd.2021.08.005.
39. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int. 2021;100(3):702-4. doi: 10.1016/j.kint.2021.06.025
40. Chen YW, Tucker MD, Beckermann KE, Iams WT, Rini BI, Johnson DB. COVID-19 mRNA vaccines and immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. Eur J Cancer. 2021;155:291-3. doi: 10.1016/j.ejca.2021.07.017
41. Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol. 2021;22(5):581-3. doi: 10.1016/s1470-2045(21)00155-8
42. ClinicalTrials.gov. A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults (ENSEMBLE 2). Last accessed: September 2021. Available at: https://clinicaltrialsgov/ct2/show/NCT04614948
43. Janssen Clinical Protocol. A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older (ENSEMBLE 2). Last accessed: September 2021. Available at: https://wwwjnjcom/coronavirus/ensemble-2-study-protocol. 2021.
44. Sadoff J, Le Gars M, Cardenas V, Shukarev G, Vaissiere N, Heerwegh D, et al. Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting. bioRxiv 2021;doi: 10.1101/2021.08.25.21262569
45. Janssen data on file. ENSEMBLE and ENSEMBLE 2 data. September 2021. 2021.
46. Burki T. Booster shots for COVID-19-the debate continues. Lancet Infect Dis. 2021;21(10):1359-60. doi: 10.1016/s1473-3099(21)00574-0 PMC8457762
47. Lie RK, Miller FG. Allocating a COVID-19 Vaccine: Balancing National and International Responsibilities.. Milbank Q 2021;99.:450-66. doi: 10.1111/1468-0009.12494
48. The Lancet Infectious D. COVID-19 vaccine equity and booster doses. Lancet Infect Dis. 2021;21(9):1193. doi:10.1016/s1473-3099(21)00486-2

49. Iftekhar EN, Priesemann V, Balling R, Bauer S, Beutels P, Calero Valdez A, et al. A look into the future of the COVID-19 pandemic in Europe: an expert consultation. Lancet Reg Health Eur. 2021;8:100185.doi: 10.1016/j.lanepe.2021.100185 PMC8321710

50. Murray CJL, Piot P. The Potential Future of the COVID-19 Pandemic: Will SARS-CoV-2 Become a Recurrent Seasonal Infection? Jama. 2021. 10.1001/jama.2021.2828

51. Kent SJ, Juno JA. Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots. EBioMedicine. 2021 Oct;72:103586. doi: 10.1016/j.ebiom.2021.103586er.

Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
doi:10.37201/req/158.2021

Pharmacological treatment of COVID-19: an opinion paper

Alberto García-Lledó[1]
Javier Gómez-Pavón[2]
Juan González del Castillo[3]
Teresa Hernández-Sampelayo[4]
Mari Cruz Martín-Delgado[5]
Francisco Javier Martín Sánchez[6]
Manuel Martínez-Sellés[7]
José María Molero García[8]
Santiago Moreno Guillén[9]
Fernando Rodríguez-Artalejo[10]
Julián Ruiz-Galiana[11]
Rafael Cantón[12]
Pilar De Lucas Ramos[13]
Alejandra García-Botella[14]
Emilio Bouza[15]

[1]Cardiology Service. Prince of Asturias Hospital. University of Alcalá. Madrid.
[2]Geriatrics Service. Central Hospital of the Red-Cross. Alfonso X el Sabio University. Madrid.
[3]Emergency Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[4]Pediatrics and ACES Service. Gregorio Marañón General University Hospital, Complutense University. Madrid.
[5]Intensive Medicine Service. Torrejón University Hospital. Francisco de Vitoria University. Madrid.
[6]Geriatrics Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[7]Cardiology Service. Gregorio Marañón General University Hospital, European University. Madrid.
[8]Family Medicine. Infectious diseases. Madrid.
[9]Infectious Diseases Service. Ramón y Cajal Hospital. University of Alcalá de Henares. Madrid.
[10]Department of Public Health. Autonomous University. Madrid.
[11]Internal Medicine Service. Ruber International Hospital. Madrid.
[12]Microbiology Service. Ramón y Cajal Hospital and Ramón y Cajal Institute for Health Research (IRYCIS). Spanish Network for Research in Infectious Pathology (REIPI). Madrid.
[13]Emeritus. Pneumology Service. Gregorio Marañón General University Hospital, Complutense University. Madrid
[14]General Surgery Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[15]Clinical Emeritus, Community of Madrid. Clinical Microbiology and Infectious Diseases Service of the Gregorio Marañón General University Hospital, Complutense University. CIBERES. Cyber of Respiratory Diseases. Madrid

Article history
Received:27 November 2021; Accepted: 6 December 2021; Published: 11 December 2021

ABSTRACT

The precocity and efficacy of the vaccines developed so far against COVID-19 has been the most significant and saving advance against the pandemic. The development of vaccines has not prevented, during the whole period of the pandemic, the constant search for therapeutic medicines, both among existing drugs with different indications and in the development of new drugs. The Scientific Committee of the COVID-19 of the Illustrious College of Physicians of Madrid wanted to offer an early, simplified and critical approach to these new drugs, to new developments in immunotherapy and to what has been learned from the immune response modulators already known and which have proven effective against the virus, in order to help understand the current situation.

Keywords: COVID-19, SARS-CoV2, treatment, Remdesivir, Favipiravir, Molnupiravir, PF-07321332, Paxlovid, convalescent plasma, Sotrovimab, Banlanivimab, Etesevimab, Casirivimab, Imdevinab, AZD7442, Ciganilmab, Tixagevimab, Evusheld, BRII-196, BRII-198, Dexamethasone, Corticosteroids, Tocilizumab, Sarilumab, Anakinra, Canakinumab, Baricitinib, Tofacitinib, Ruxolitinib, Adalimumab, Certolizumab, Infliximab, Etanercept, Golimumab, Itolizumab, Ravulizumab, Lemilumab, Ivermectin, Colchicine, Vitamin D, Metformin, Fluvoxamine, Azithromycin, Hydroxychloroquine, Lopinavir/Ritonavir.

Correspondence:
Emilio Bouza
Servicio de Microbiología Clínica y Enfermedades Infecciosas del Hospital General Universitario Gregorio Marañón, Universidad Complutense. CIBERES. Ciber de Enfermedades Respiratorias. Madrid
E-mail: emilio.bouza@gmail.com

All authors belong to the Scientific Committee on COVID-19 of the Madrid College of Physicians (ICOMEM).

Tratamiento farmacológico del COVID-19: un documento de opinión

RESUMEN

La precocidad y la eficacia de las vacunas desarrolladas hasta ahora frente al COVID-19, ha sido el avance más significativo y salvador frente a la pandemia. El desarrollo vacunal no ha impedido, durante todo el periodo de la pandemia, la búsqueda constante de remedios terapéuticos, tanto entre los medicamentos ya existentes y con indicaciones diversas, como en el desarrollo de nuevos fármacos. Sobre estos nuevos fármacos, sobre las novedades en la inmunoterapia y sobre lo aprendido de los moduladores de la respuesta inmune ya conocidos y que se han mostrado eficaces frente al virus, el Comité Científico del COVID-19 del Ilustre Colegio de Médicos de Madrid ha querido ofrecer una aproximación precoz, simplificada y critica que pueda ayudar a comprender la situación actual.

Palabras clave: COVID-19, SARS-CoV2, tratamiento, Remdesivir, Favipiravir, Molnupiravir, PF-07321332, Paxlovid, plasma de convalecientes, Sotrovimab, Banlanivimab, Etesevimab, Casirivimab, Imdevinab , AZD7442, Ciganilmab , Tixagevimab, Evusheld, BRII-196, BRII-198, Dexametasona, Corticosteroides, Tocilizumab, Sarilumab, Anakinra, Canakinumab, Baricitinib, Tofacitinib, Ruxolitinib, Adalimumab, Certolizumab, Infliximab, Etanercept, Golimumab, Itolizumab, Ravulizumab, Lemilumab, Ivermectina, Colchicina, Vitamina D, metformina, Fluvoxamina, Azitromicina, Hidroxicloroquina, Lopinavir/Ritonavir.

INTRODUCTION

With the achievement of useful vaccines against COVID-19, whose efficacy is extraordinarily high but not absolute, and in view of the possibility that new variants of the virus may limit its efficacy, it is pertinent to turn our attention from the preventive to the therapeutic sphere. In addition, there is still a large number of unvaccinated persons. In the case of children aged 5 to 11 years, the European Medicines Agency (EMA) has approved the Comirnaty vaccine on 25 November 2021 [1].

The treatments against the disease are beginning to bear objective and significant fruit both in the field of direct antiviral therapy and in that of anti-inflammatory and immunotherapeutic treatment. A good example of this is the repositioning of monoclonal antibodies or the presentation of new effective antiviral agents that can be administered orally.

The Scientific Committee of COVID-19, of the Illustrious College of Physicians of Madrid (ICOMEM) has received and has been asked several questions about the present reality of the pharmacological treatment of COVID-19, to which the group has tried to give answers, after deliberation and consensus.

This document is not intended to be an exhaustive review of the state of the art of pharmacological treatment of the disease caused by SARS-CoV-2, but rather to offer a current, summarized and easily understandable perspective that includes the situation in Spain.

In the following pages we have compiled the scientific evidence that we have been able to collect, also providing the opinion of the ICOMEM working group.

1. SOME CLINICALLY EFFECTIVE ANTIVIRALS AGAINST COVID-19

In a disease of viral etiology, with some very aggressive and rapidly evolving forms, it is logical that drug treatments with antiviral activity began to be used early and, to a certain extent, indiscriminately, from the onset of the pandemic. We will confine ourselves here to listing those that have shown some efficacy in clinical trials or that seem very promising in this respect.

Remdesivir is a prodrug in monophosphate form that is metabolized to active adenosine triphosphate. It inhibits the replication of several families of RNA viruses, including coronaviruses. This drug had been studied against Ebola and Marburg viruses and clinical trials in SARS-CoV-2 infection started early [2-9]. Preclinical data showed that early treatment could decrease viral load, reduce lung damage and improve survival.

To date, although the drug has been approved for severe patients by the FDA and EMA, the results cannot be considered uniformly conclusive as some clinical trials have shown discordant results [5-11]. The first randomized, placebo-controlled, phase III clinical trial with remdesivir was published in 2020. It included 237 patients, with severe disease and O_2 desaturation, who received treatment for 10 days. In this first trial, no clinical benefits were obtained, but a trend towards improvement was observed when treatment was started early. [12]. Negative results were also found within the Solidarity study in which 405 hospitals in 30 countries participated. A total of 11,330 patients were included in different groups, of whom 2,750 were assigned to remdesivir. No improvement in clinical outcome or mortality was observed in this study [13]. In the multi-center DisCoVeRy study, which included more than 800 patients [14] no clear benefit was demonstrated either. However, in the ACTT-1 study, with more than 1,200 randomized patients, a more rapid clinical improvement was demonstrated in patients receiving remdesivir versus placebo and even a reduction in all-cause mortality. This trial led to FDA approval of the drug [15].

In a meta-analysis that included 5 randomized, placebo-controlled clinical trials with a total of 13,594 patients, those treated with remdesivir showed a more rapid clinical improvement and a reduction in the number of days of hospitalization. The differences in mortality were not significant, although there was a trend in that direction in the 5-day treatment studies [5].

In an observational study carried out in Spain at the Hospital Clínico de Barcelona, the use of remdesivir improved survival, with greater efficacy in patients who received treatment earlier, with a total reduction in the risk of death of 62% [16]. Other studies showed similar results, such that treated patients had less need for mechanical ventilation and lower mortality [17,18].

Remdesivir is therefore included as an effective drug in guidelines such as that of the Spanish Society of Infectious Diseases (SEIMC), indicated for patients in severe but not critical condition, with less than ten days of evolution. Similarly, the IDSA recommends remdesivir in hospitalized patients but not in critically ill patients [19,20].

Recent studies have shown a decrease in the combined endpoint of COVID-related hospitalization and all-cause death of 87% in outpatients at high risk of progression treated for 3 days with remdesivir [21].

Favipiravir is a nucleoside, prodrug, antiviral, broad-spectrum, RNA-dependent, RNA polymerase-dependent antiviral drug that has already been used in the treatment of influenza and studied against SARS-CoV-2, preferably in Japan and other Asian countries [22].

It has been compared, in small studies, with drugs whose ineffectiveness has been proven a posteriori, without showing significant differences. Such is the case with hydroxychloroquine [23], lopinovir/ritonavir [24] , inhaled ß interferon [25] and with baloxavir [26] .

Finally, in a randomized, open-label, phase 3 study in cases of mild or moderate COVID, again with few cases (150 patients), a comparison was made with standard treatment, without the study allowing, in our opinion, any clear conclusion to be drawn [27].

For all these reasons, in our opinion, this drug does not yet have a study that establishes a clear efficacy and must still be considered among the experimental drugs [28, 29].

Molnupiravir, an orally administered drug, has recently been approved at least in the United Kingdom and the United States for use in patients with mild to moderate COVID-19. It is a prodrug with activity against RNA viruses. Preclinical animal studies have shown efficacy, with a broader spectrum than even remdesivir, and Phase I human clinical trials have shown good levels of safety [30]. A phase II clinical trial has proven its efficacy in terms of viral clearance at 7 days [31], including pharyngeal clearance of viruses.

Preliminary data from Phase III studies have revealed a significant reduction in the rate of disease progression, hospitalizations, need for ICU and death in the group of patients starting with mild or moderate disease. In contrast, no significant results are obtained in patients with advanced and severe disease [32].

Readers interested in more information on this new drug can find it in the following references [33-39].

PF-07321332 (Paxlovid®, Pfizer), is a ritonavir-boosted protease inhibitor that would reduce the risk of hospitalization or death in 90% of subjects with mild to moderate disease.

PF -07321332 targets the major protease (Mpro) of SARS-COV-2 that processes the two polyproteins through at least 11 cleavage sites. The amino acid sequence and three-dimensional structure of Mpro are highly conserved across the Coronavirinae subfamily, providing a strong basis for the design of therapeutics to target potentially immune-evasive SARS-CoV-2 variants [40,41].

Pfizer has just announced at a press conference that its product Paxlovid® (PF-07321332 + ritonavir) reduces the risk of hospitalization or death by 89%, compared to placebo, in adults not hospitalized but at high risk of poor outcome at the conclusion of its EPIC study (Phase 2/3). The data will be submitted to the U.S. FDA for emergency use authorization (EUA) as soon as possible [42]. In patients treated within 3 days of symptom onset (primary endpoint); 0.8% of patients receiving Paxlovid® required hospitalization in the first 28 days (3/389 hospitalized, no deaths), compared to 7.0% of patients receiving placebo (27/385 hospitalized with 7 subsequent deaths). The primary analysis of the interim dataset evaluated 1,219 adults enrolled through September 29, 2021. At the time the decision was made to discontinue patient recruitment, enrollment was at 70% of the planned 3,000 patients. Treatment-emergent adverse events were comparable between Paxlovid® (19%) and placebo (21%), most of which were mild in intensity.

2. CONVALESCENT PLASMA AND IV IMMUNOGLOBULINS

Immunoglobulins and convalescent plasma (CP) is obtained from persons who have recovered from COVID-19. Since the primary host immune response appears 10 to 14 days after infection, plasma should be collected from donors no earlier than the second or third week after SARS-CoV-2 infection [43].

Plasma would provide passive immunity based on antibodies and therefore could reduce both the severity and duration of the disease, so it could be indicated in hospitalized patients and with special interest in immunosuppressed patients with deficient antibody production. As a human blood product it can cause the same reactions as transfusions (allergic and anaphylactic reactions, hemolysis, fluid overload, etc.), but studies consistently show that plasma transfusion is safe with effects similar to those of ordinary transfusions [44-51].

However, despite the justification for its use, the experience in other viral epidemics and its safety, there are still no clear results in terms of efficacy. It began to be used in moderate-severe COVID-19 with publication of observational studies and clinical trials [46-48], with systematic review and meta-analysis [45,46], which have provided inconclusive results. Furthermore, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g. in terms of antibody content and stratification of recipient patients according to their serological status).

Given these findings, the FDA argued that a "totality of evidence" suggested that the benefits of convalescent plasma would outweigh its risks and, given the lack of effective treatments, granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients with signs of progressive infection [44].

Outside the U.S., a randomized, open-label, controlled clinical trial in 27 hospitals in Spain is worth mentioning [49] in which no differences were obtained in terms of overall mortality (11.7% in the treated group vs. 16.4% in the control group, p = 0.205), nor in terms of progression at 14 days. The PLACID study, carried out in India [50], also failed to demonstrate a decrease in disease progression and mortality. In summary, at the present time, convalescent plasma is not a treatment approved by the European Medicines Agency and even uncontrolled compassionate use of this procedure should be discouraged.

3. MONOCLONAL ANTIBODIES USABLE IN MONOTHERAPY

The world of monoclonal antibodies and the data on their activity have had a very important boost recently and we consider them to be an area of great interest. In this section we will discuss sotrovimab, which is indicated for monotherapy.

Sotrovimab. It is a recombinant engineered humanized monoclonal antibody (IgG) that binds with high affinity to a highly conserved epitope in the receptor binding domain (RBD) of the S protein (spike) of SARSCoV-2. Its exact mechanism of action is not well understood, but it appears to prevent fusion

after the virus binds to the human angiotensin 2-converting enzyme receptor (ACE_2).

Interim results from the COMET-IC (Early Treatment of COVID-19 in Outpatients) Phase II clinical trial were published in October 2021 [52]. This multicenter, double-blind trial evaluated the clinical course after administration of a single intravenous infusion of sotrovimab in 291 adult patients diagnosed with mild to moderate COVID-19 (Sat 02 ≥94% on room air), not hospitalized, within the first 5 days of symptom progression versus a placebo group of 292 infected. Patients included in the trial were 18 years of age or older and were at high risk for progression of COVID-19 because of their age (≥55 years) or because they had at least one risk factor for progression to severe disease [52]. The primary efficacy outcome was hospitalization (for > 24 hours) for any cause or death within 29 days after randomization. The use of sotrovimab was associated with an 85% reduction in the relative risk of progression to severe or critical illness and up to a 79% reduction in the risk of all-cause hospitalization or death through day 29. In addition, no safety issues were identified that compromised treatment [52].

In May 2021, the FDA authorized the emergency use of sotrovimab in the US [53]. In Europe, it is part of the European Commission's portfolio of promising treatments against COVID-19 [54]. In May 2021, the Committee for Medicinal Products for Human Use (CHMP) issued its positive opinion on the drug, following review of data from the interim analysis of data from the Phase III Comet-ICE study [55] and will be studied by the European Medicines Agency (EMA) for possible authorization.

The COMET study demonstrated that intramuscular administration of sotrovimab is not inferior and offers similar efficacy to the intravenous formulation in a population at high risk of poor outcome. IM administration may facilitate its administration in primary care.

4. MONOCLONAL ANTIBODIES USED IN COMBINATION

Bamlanivimab + etesevimab. In November 2020, the IgG1 neutralizing monoclonal antibody bamlanivimab (LY-CoV555; Lilly) received emergency use authorization (EUA) from the FDA for the treatment of newly diagnosed mild to moderate COVID-19 in patients 12 years of age and older, body weight equal or superior to 40 kg, in good baseline condition but at high risk for progression to severe disease or requiring hospitalization [56].

Subsequently, in April 2021 the FDA revoked the US clearance of the monotherapy, due to the progressive increase of COVID-19 cases in the US caused by SARS-CoV-2 variants resistant to such monotherapy [57].

This revocation did not affect the combined use of bamlanivimab and etesevimab, which maintained its indication for emergency use. In a phase 3 clinical trial comparing single intravenous administration of the combination of bamlanivimab and etesevimab versus placebo within 3 days of laboratory confirmation of SARS-CoV-2 infection, the combination led to a lower incidence of COVID-19-related hospitalization and death from any cause on day 29 and accelerated the decline in SARS-CoV-2 viral load [58].

In the trial (BLAZE-1), the mean decrease in SARS-CoV-2 viral load at day 11, the primary endpoint, was significantly greater with bamlanivimab plus etesevimab than with placebo. Hospitalization for COVID-19 or death from any cause at day 29 occurred significantly less frequently with the antibody combination than with placebo (2.1% vs. 6.6%; HR 0.32; NNT 22.5). No deaths occurred in the antibody group, compared with 10 in the placebo group [59].

In a second trial (BLAZE-4), the FDA selected 700 mg/1400 mg as the licensed dose for use of bamlanivimab and etesevimab together, prompting the manufacturer to study this dose in a new cohort (BLAZE-1.5). The rate of hospitalization for COVID-19 or death from any cause at day 29 was significantly lower with the antibodies than with placebo (0.8% vs. 5.4%; HR 0.13; NNT 21.5).

Bamlanivimab and etesevimab should be administered as soon as possible after a positive SARS-CoV-2 test result and within 10 days of the onset of COVID-19 symptoms. Patients should be treated in a facility staffed and equipped for the management of anaphylaxis and should be monitored for hypersensitivity reactions during drug administration and for at least 1 hour after completion of the infusion.

In March 2021, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA), began the ongoing review procedure of the results of studies with bamlanivimab and etesevimab, for the treatment of confirmed COVID-19. The review ended without issuing the conclusions, once the company Eli Lilly Netherlands BV, the marketer of the two molecules, informed the Agency on October 29, 2021 that it was withdrawing from the process [60]. In its letter notifying the Agency of the withdrawal, the company stated that it was withdrawing because EMA required prospective concurrent validation data that could only be generated through the production of new batches of active substance and that it was not in a position to generate such additional data.

This product has been withdrawn from the evaluation process in Europe.

Casirivimab + imdevimab. Regeneron's monoclonal antibodies casirivimab (REGN10933) and imdevimab (REGN10987) are cleared for use together.

The FDA has cleared this combination of monoclonal antibodies to SARS-COV-2 on an emergency basis (REGEN-COV) for co-administration by intravenous or subcutaneous injection for the treatment of mild to moderate COVID-19 in individuals over 12 years of age and weighing no less than 40 kg who are at high risk for progression to severe COVID-19 [61,62]. Traditional risk groups would also include overweight patients or pregnant women, as well as those suffering from cardiovascular disease, hypertension or chronic respiratory disease (Table 1) [61,63,64].

In contrast, this combination could worsen the results if administered to patients hospitalized for COVID-19 or requiring high-flow oxygen or mechanical ventilation.

The mechanism of action is based on the fact that casirivimab and imdevimab bind to different sites of the receptor-binding domain of the SARS-CoV-2 spike protein, blocking its binding to the human ACE2 receptor.

FDA clearance was based on interim Phase 1/2 results from a double-blind trial (COV-2067) in which 799 outpatients with mild to moderate COVID-19 were randomized in a blinded fashion to receive a single intravenous infusion of monoclonals or placebo. Outcomes were assessed 28 days after infusion [64] and viral load at day 7 was significantly lower with the monoclonal combination than with placebo. There was also less need for hospitalization, emergency department visit or teleconsultation within 28 days after infusion (2.8% vs. 6.5%). Among patients at higher risk of disease progression, rates of poor outcome were 3% with casirivimab and imdevimab and 9% with placebo. The combination is protective against variants of concern known to date [65].

Subsequent data in Phase 3 studies (COV-2067), in which 3,867 patients with mild or moderate COVID and at least one risk factor for progression to severe disease were randomized prompted the FDA to change the licensed dose of casirivimab and imdevimab from 1200 mg to 600 mg of each antibody [64,66].

We are not aware of studies comparing this combination with other monoclonal antibody combinations. Anaphylaxis reactions have occasionally been detected with this combination, although they are very rare [64].

If intravenous infusion is not feasible and would result in a delay in treatment, casirivimab and imdevimab can be administered subcutaneously. The licensed dose is 600 mg of casirivimab and 600 mg of imdevimab administered in four consecutive 2.5-ml injections (2 injections of each antibody packaged separately, or 4 injections of the co-formulated formulation) at different sites on the thigh, back of the arm, or abdomen (except 5 cm around the umbilicus). If a prepared syringe cannot be used immediately after dilution, it can be refrigerated or left at room temperature for up to 4 hours. If refrigerated, the syringe should remain at room temperature for 20 minutes before administration.

Casirivimab and imdevimab should be administered in a facility staffed and equipped to manage anaphylaxis. Patients should be monitored for hypersensitivity reactions for at least 1 hour after antibody administration.

The combination of casirivimab and imdevimab has been administered with good tolerance to pregnant women [67].

In May 2021, the FDA has extended clearance for the use of the combination of casirivimab and imdevimab to post-exposure prophylaxis in high-risk individuals if they are not fully vaccinated or if they have a poor immune response to the vaccine [68, 69].

This indication expansion is based on the results of a randomized, double-blind, placebo-controlled trial in 1,505 healthy, unvaccinated patients aged ≥12 years with no evidence of prior immunity who were household contacts of persons with SARS-CoV-2 infection (positive test within the previous 96 hours). Patients received a single subcutaneous dose of casirivimab and imdevimab (600 mg each) or placebo. Symptomatic SARS-CoV-2 infection within 4 weeks of randomization was significantly lower in patients who received the antibodies than in those who received placebo (1.5% vs. 7.8%). Among patients who developed symptomatic infection, the duration of symptoms was significantly shorter in the antibody group (mean 1.2 vs. 3.2 weeks with placebo). There were no hospitalizations or emergency department visits due to COVID-19 in the antibody group compared to 4 in the placebo group [70].

AZD7442: Cilgavimab (AZD1061) + Tixagevimab (AZD8895) (Evusheld). AZD7442 is a combination of two monoclonal antibodies from Astra Zeneca, AZD8895 (tixagevimab), a long-acting agent, and AZD1061 (cilgavimab), which simultaneously bind to distinct non-overlapping epitopes in the protein S receptor binding domain to neutralize SARS-CoV-2. Both form a complex with the receptor binding domain (RBD) and have strong neutralizing activity against SARS-CoV-2 and variants with antigenic substitutions at the RBD [71].

They are currently being evaluated for single-dose administration (intramuscular or intravenous) to treat or prevent COVID-19. Preliminary results in treatment suggest a decrease in severity in patients. Applied to both pre-exposure and post-exposure prevention, the results of the studies are scheduled for completion in June 2022 [72].

Preliminary results of the preventive treatment have been reported by Astra Zeneca, announcing that AZD-7442 failed to improve outcomes in SARS-CoV-2 post-exposure prophylaxis. On the contrary, in pre-exposure prophylaxis, the study suggests its efficacy in reducing the risk of developing symptomatic COVID-19 by 77%. Protection could be maintained for up to 12 months.

Combination of neutralizing monoclonal antibodies BRII-196 and BRII-198. BRII-196 and BRII-198 are noncompetitive anti-SARS-CoV-2 monoclonal antibodies. They reduce virus binding to the receptor and their structure allows for a long half-life of activity, according to data from a study (ACTIV-2), sponsored by NIAID and led by the ACTG.

A study evaluates the safety/efficacy of investigational agents for the treatment of non-hospitalized adults with mild-moderate COVID-19 under a randomized, blinded, controlled, adaptive platform. BRII-196/BRII-198 (1,000 mg each) is administered as single doses in sequential infusions to patients at high risk for clinical progression (i.e., age ≥ 60 years or presence of other medical conditions) within 10 days of symptom onset and after positive test for SARS-CoV-2. The primary endpoint was hospitalization and/or death through day 28.

Between January and July 2021, 837 participants (418 active, 419 placebo) in various nations were randomized and

received study product at the time when emerging variants were circulating. In the interim analysis, the BRII-196/BRII-198 combination had fewer hospitalizations (12 vs. 45) and deaths (1 vs. 9 AZD7442) compared to placebo. Grade 3 or higher adverse events (AEs) were observed less frequently among participants on BRII-196/BRII-198 than on placebo (3.8% vs. 13.4%), with no serious infusion or other reactions.

Thus, the BRII-196/BRII-198 combination appears safe, well tolerated, and demonstrated a significant reduction compared to placebo in the risk of hospitalization and/or death among adults with mild-moderate COVID-19 at high risk of progression to severe disease [73].

5. THE ROLE OF CORTICOSTEROIDS IN THE TREATMENT OF SEVERE COVID-19

The use of dexamethasone is recommended in critically ill patients with COVID 19 who require oxygen therapy or ventilatory support. The recommended dose is 6 mg daily for 10 days or until hospital discharge. Comparison of dexamethasone 12 mg daily versus 6 mg has shown no difference in the results regarding efficacy (survival without life support at 28 days) and safety in the most critically ill patients [74]. If dexamethasone is not available, other glucocorticoids at equivalent doses (total daily doses of hydrocortisone 160 mg, methylprednisolone 32 mg or prednisone 40 mg) may be considered, although the data supporting the use of these alternatives are more limited than those for dexamethasone [75-77]. In contrast, the use of dexamethasone (or other glucocorticoids) is not recommended for the prevention or treatment of mild to moderate COVID-19 (patients not receiving oxygen).

The World Health Organization (WHO) [77] has established two recommendations regarding the use of corticosteroids in COVID-19 patients:

1. Administration of systemic corticosteroids in preference to no administration for the treatment of severe and critically ill patients (strong recommendation, based on moderate certainty evidence).

2. Refraining from the use of corticosteroids in the treatment of non-critically ill COVID-19 patients (conditional recommendation, based on low certainty evidence).

This guideline is based on a reduction in 28-day mortality of 8.7% and 6.7% in critically or severely ill COVID-19 patients. In addition, systemic corticosteroids probably reduce the need for invasive mechanical ventilation [77]. The oxygen saturation threshold of 90% for the definition of severe COVID 19 is considered arbitrary and is recommended to be adjusted to the patient's baseline situation.

The main study supporting these recommendations is Recovery [78] which shows a reduction in 28-day mortality in patients with COVID 19 with mechanical ventilation (29.3% vs. 41.4%) or oxygen therapy (23.3% vs. 26.2%) but not in patients without respiratory support (17.8% vs. 14.0%). The main adverse events related to the use of corticosteroids have been related to hyperglycemia and hypernatremia [79] , as well as with new episodes of septic shock, invasive fungal infections, *Strongyloides stercoralis* hyperinfection in endemic areas, and gastrointestinal bleeding. As of April 2021, 42 clinical trials of corticosteroids in severe COVID-19 patients were ongoing and 16 had been completed but not published, possibly increasing the evidence available in the immediate future [79].

The use of corticosteroids in persistent COVID-19 interstitial lung disease has shown benefits in some observational series but clinical trials are needed to confirm these results [80].

6. OTHER IMMUNOMODULATORY DRUGS

Cytokine production in response to viral replication plays an important role in lung damage, in the need for mechanical ventilation and, globally, in the survival of patients with COVID-19. This has prompted research into the efficacy of immunomodulatory drugs that limit cytokine-associated effects. The demonstration of the beneficial effects of corticosteroids in patients with severe pneumonia reinforces anti-inflammatory/immunomodulatory therapy as a way to address severe disease.

The immunomodulatory drugs investigated are grouped into several families according to their mechanism of action (Table1). Of these, only a few have sufficient data to be able to make a judgment on their use in COVID-19.

Table 1 **Immunomodulatory drugs investigated in the treatment of COVID-19.**

Class (Mechanisms of action)	Drugs
IL-6 inhibitors	Tocilizumab
	Sarilumab
IL-1 antagonists	Anakinra
	Canakinumab*
Bruton's Tirosin Kinase (BTK) inhibitors	Acalabrutinib*
Janus Kinase (JAK) inhibitors	Baricitinib
	Tofacitinib
	Ruxolitinib*
TNF inhibitors	Adalimumab*
	Certolizumab*
	Infliximab*
	Etanercept*
	Golimumab*
Anti CD_6 monoclonal antibodies	Itolizumab*
C5 complement inhibitors	Ravulizumab*
GM-CSF inhibitors	Lemilumab*

*** There is not enough data to consider its use.**

The drugs whose clinical trials and observational studies have shown results that make their use worth considering are grouped into three families: IL-6 inhibitors, IL-1 antagonists and JAK inhibitors.

The most widely evaluated IL-6 inhibitor is tocilizumab. Initial results from observational studies were very encouraging, but were not always followed by similar results in clinical trials. The registry clinical trials (COVACTA, EMPACTA) failed to show benefit in patients with severe pneumonia, including patients requiring ICU admission or mechanical ventilation [81-85]. Some subsequent clinical trials showed that tocilizumab administration in patients with severe pneumonia is associated with a significant decrease in mortality and organ support-free time. [86-88]. Significantly, the RECOVERY study showed that tocilizumab was effective in reducing mortality in patients with inflammation data (CRP >75 mg/L in this study) [89], similar to some observational studies [90,91]. Of particular importance was that the benefits of tocilizumab were felt even when the patient was receiving steroids. The positive results of these clinical trials have led most COVID-19 treatment guidelines to include it as an option in patients with severe pneumonia, especially if they have elevated markers of inflammation. Sarilumab is another IL-6 inhibitor that has been evaluated in clinical trials. The number of patients treated does not allow conclusions to be drawn and, at this time, it is recommended for use only in patients who for whatever reason cannot receive tocilizumab.

Among the JAK inhibitors, baricitinib and tofacitinib have obtained positive results in clinical trials. Both drugs have shown a decrease in progression to mechanical ventilation and mortality, independent of concomitant steroid use [92-95].

Finally, an IL-1 inhibitor, anakinra, has also shown beneficial effects on clinical progression and mortality in patients with severe pneumonia [96-98]. In a double-blind clinical trial, the drug demonstrated benefit especially in patients who had elevated suPAR levels (>6 ng/mL), a marker of severity in patients with COVID-19 [99].

There is no doubt that the group of drugs we are discussing have a role in the treatment of patients with severe COVID-19 pneumonia. It should be noted that, in a recent review, baricitinib and tofacitinib were included, along with dexamethasone and tocilizumab, as the drugs that had demonstrated a decrease in COVID-19-associated mortality in randomized clinical trials [95].

It is possible that anakinra could be added to this list. The timing of administration also seems to be well established. It should not be administered during the early stages of the disease, when antiviral drugs are preferentially indicated, and should be reserved for patients requiring oxygen therapy. Both dexamethasone and tocilizumab could also be administered in patients requiring mechanical ventilation or ECMO. Both JAK inhibitors and IL-6 inhibitors can and should be administered in conjunction with dexamethasone in patients in whom they are indicated.

Some doubts remain to be resolved. No comparative studies have been carried out between the different options and the profile of patients who can benefit optimally from each of them remains to be determined. The elevation of some plasma markers may help to make the decision. Elevated IL-6 and CRP have been shown to be suitable markers to identify patients who benefit from tocilizumab, suPAR has been shown to identify patients who benefit from anakinra. It is also not known whether the association of more than one of these immunomodulatory drugs adds any advantage to the isolated administration of each of them. The target on which they act is different, which could determine synergism with potentiation of the benefits.

7. KNOWN DRUGS WITH OTHER INDICATIONS UNDER EVALUATION FOR COVID-19

Ivermectin. Ivermectin is a broad-spectrum antiparasitic agent that has been shown to be effective against SARS-CoV-2 in vitro [100]. Ivermectin is approved in some countries for the treatment of parasitic infections, but not for COVID-19. In particular, the World Health Organization does not recommend the use of this drug except in the context of a clinical trial [101] and other studies advise against its use [102-104].

Colchicine. Colchicine is a potent agent that inhibits multiple proinflammatory pathways, so it was thought that it could be useful in the control of the inflammatory complications of COVID-19. Colchicine is approved in some countries, such as Spain, for the treatment of gout and familial Mediterranean fever, but not for COVID-19, as it is considered that there is insufficient evidence of its usefulness, and it also has significant adverse effects, especially gastrointestinal. [105,106]. Therefore, it can only be used for the treatment of COVID-19 within a clinical trial.

Vitamin D. Vitamin D supplementation has been associated with lower risk of acute respiratory infections, such as influenza [100]. However, there are insufficient data to recommend or reject the use of vitamin D for the prevention or treatment of COVID-19 [107]. A Cochrane review found a large heterogeneity of studies on this vitamin in the treatment of COVID-19, due to the different supplementation strategies, formulations, vitamin D level of the participants and the results found [108]. It is noteworthy that one of the first clues to the potential usefulness of vitamin D in COVID-19 was a pilot randomized controlled trial conducted in Spain, which observed that high-dose calcifediol reduces the need for intensive care unit treatment in patients hospitalized for COVID-19 [109].

Metformin. Metformin is a first-line treatment for type 2 diabetes, but it has also shown some efficacy in infectious diseases, such as influenza and hepatitis C. In a July 2021 review, 4 observational studies were identified that showed a reduction in mortality among people using metformin on an outpatient basis [110]. However, the evidence is insufficient to recommend the use of this drug to reduce COVID-19-associated mortality [111].

Fluvoxamine. Fluvoxamine is an antidepressant drug (selective serotonin reuptake inhibitor and -1 receptor agonist) that also has certain anti-inflammatory and possibly antiviral effects. On October 27, 2021, the results of the TOGETHER trial, which is the largest randomized trial to date (741 patients on fluvoxamine and 756 on placebo) to evaluate the effectiveness of this drug in symptomatic patients with COVID-19 at high risk of developing severe COVID-19 in Brazil, were published on October 27, 2021 [112]. Compared to those treated with placebo, patients with fluvoxamine (100 mg twice a day for 10 days) reduced by 38% the frequency of hospitalization, defined as a stay of more than 6 hours in a COVID-19 emergency device or transfer to a tertiary hospital due to COVID-19. These results are very encouraging because of the high efficacy of the treatment, and because it is oral and very low cost, but they need to be replicated in new studies.

8. DRUGS DISCARDED AFTER PROVING INEFFECTIVENESS

Among the drugs that have been massively used and have now been shown to be ineffective, we would like to highlight hydroxychloroquine/chloroquine, azithromycin, and lopinavir/ritonavir. We will now detail what motivated their use and why they are no longer in use.

Hydroxychloroquine and chloroquine are drugs approved for the treatment of lupus erythematosus, rheumatoid arthritis and malaria. They were among the first treatments used at the beginning of the pandemic. Hydroxychloroquine was thought to be more effective due to the results of in vitro experiments and pharmacokinetic models. However, published studies do not indicate that they have antiviral efficacy, nor do they improve clinical course or mortality. Neither the Solidarity clinical trial (CT) [113], nor Recovery [114], have shown benefit. The pooled relative risk of mortality from these trials was 1.11, 95% CI 0.99-1.24, with no apparent benefit in both ventilated and nonventilated patients. This CI excludes any benefit of hydroxychloroquine in hospitalized patients. These trials also do not demonstrate excess mortality in relation to the use of hydroxychloroquine in hospitalized patients [113,114].

Azithromycin has, in addition to its bacteriostatic activity, an immunomodulatory, anti-inflammatory, and antiviral effect [115,116]. It can also improve patients with respiratory distress syndrome [117, 118]. Based on these facts, it has been used empirically in patients with COVID, especially in moderate-severe cases. Its use has also been justified with the intention of reducing bacterial superinfection in critically ill patients. A systematic review and meta-analysis of all types of clinical studies (including 17 papers) found no clinical improvement in patients with COVID-19 [119]. No statistically significant differences were found in the rate of mortality, mechanical ventilation or hospital admission between the control group and the group treated with azithromycin. In terms of safety, the use of this macrolide has a relatively safe profile. The risk of QT prolongation was also not statistically significant compared to previous studies [119].

Lopinavir/ritonavir is used for the treatment of human immunodeficiency virus (HIV-1). It was thought to be a potential treatment for SARS-COV-2, and was shown *in vitro* to achieve inhibition of several respiratory viruses, including SARS-CoV-1, and Middle East Respiratory Syndrome (MERS) [120, 121]. However, the scientific evidence does not support its clinical use in COVID-19. A systematic review and meta-analysis evaluating the effects of lopinavir/ritonavir alone or in combination with other therapies do not report positive clinical effects [120]. Nor have larger clinical trials (RECOVERY and SOLIDARITY) demonstrated a reduction in mortality, initiation of invasive mechanical ventilation, or duration of hospitalization with this therapy. Adverse events were reported more frequently for lopinavir/ritonavir (n = 84) compared to both other antivirals and placebo [120].

In conclusion, hydroxychloroquine/chloroquine, azithromycin, and lopinavir/ritonavir although they have been widely used, are currently discarded for the treatment of COVID, since after large studies with large populations they have not shown benefit.

9. PECULIARITIES OF THE USE OF ANTI-COVID DRUGS IN PREGNANT WOMEN AND CHILDREN

In the current COVID-19 pandemic scenario, both women of childbearing age and pregnant women are a very large population at risk for SARS-COV-2 infection [122]. The situation of physiological immunotolerance of pregnancy seems to increase the risk of infection and serious complications [123], and there are more obstetric complications and higher rates of prematurity [124, 125].

The multiple safety barriers to include pregnant women in clinical trials, and the physiological changes of pregnancy, make it difficult to study new drugs in this population group [126-128].

We could summarize the drugs used for COVID in pregnant women in 3 groups [127] :

1.- Drugs that have not demonstrated efficacy against COVID-19, as listed in another section of this document, including hydroxychloroquine, chloroquine, lopinavir/ritonavir, Colchicine and Azithromycin.

2.- Drugs prohibited in pregnancy due to toxicity and teratogenic effect already known: thalidomide, and hypotensive drugs that act at the level of the renin angiotensin system and affect fetal renal development.

3.- New drugs, immunomodulators, with little knowledge in pregnant women. Among them are: tocilizumab. There is little experience with the use of tocilizumab in pregnant women with rheumatic disease and experts only recommend it if the benefit outweighs the potential risks [126].

Beta Interferon, a cytokine of the interferon family with

antiviral antiproliferative and immunomodulatory activity, used in the treatment of maternal multiple sclerosis, has been proposed for the treatment of severe cases of COVID-19 but there are no recommendations for use in COVID-19 infected pregnant women. Remdesivir has insufficient experience in pregnant women. Finally, other drugs not specifically anti-COVID-19 used in the management of pregnant women such as fluorinated glucocorticoids (betamethasone or dexamethasone), used for fetal lung maturation if indicated, and methyl prednisolone and dexamethasone have been evaluated in prospective studies and have demonstrated efficacy in the treatment of severe maternal SARS-COV2 infection [125].

It is essential to remember the need to include pregnant women in clinical trials in order to have data that allow the use of already available and future drugs with safety and certainty of effectiveness, without having to do it in compassionate use or by extrapolation of data obtained in other population groups, or used with other indications [126].

SARS-COV-2 infection in children accounts for 10% of reported cases of COVID-19. [129, 130]. Although the majority of infected children do not require specific treatment for the virus, it should be remembered that between 4 and 8% may require admission to the ICU [131-138].

Regarding treatment of COVID-19 in children, there are no data from large randomized, placebo-controlled clinical trials, and there are few observational studies to provide sufficient information to dictate treatment recommendations for COVID-19 in the pediatric population. The NIH Clinical Guidelines for treatment of COVID-19 contain specific recommendations and considerations for pediatric populations as dictated by an Expert Panel on the subject [139].

In summary:

Remdesivir is FDA cleared for the treatment of COVID-19 in children over 12 years of age, weighing more than 40kg. Also available on an emergency basis FDA (USA) for treatment of COVID-19 in hospitalized young children weighing between 3.5 kg and 40 kg, or under 12 years of age weighing more than 3.5 kg. [140].

Dexamethasone is recommended by an Expert Panel in hospitalized children with COVID-19 who require high-flow oxygen therapy, noninvasive ventilation, mechanical ventilation, or extracorporeal oxygenation (ECMO) (BIII). In contrast, it is not recommended in children who require little supplemental oxygen (nasal goggles).

3.- With monoclonal antibodies there is insufficient evidence for the recommendation or rejection of the use of this medication in children [141].

4.- COVID-19 convalescent plasma: Not recommended in hospitalized children on COVID-19, who do not require mechanical ventilation, unless administered in the course of a clinical trial (AIII). It is also not recommended for use in hospitalized children hospitalized with COVID-19 on mechanical ventilation (AIII). There are insufficient data on efficacy and safety. It could only be considered on an individual basis, in cases consulted with pediatric infectious disease specialists, using gamma globulin with high doses of immunoglobulin and patients who meet the criteria for its use.

5.- The evidence is insufficient to recommend or reject the use of tocilizumab in children.

6.- An expert panel speaks out against the use of sarilumab in hospitalized children with CONVID-19 or PIMS outside the context of a clinical trial.

7.- Post-COVID pediatric hyperinflammatory syndrome (PIMS) is a rare but serious complication in older children and adolescents. It should be treated by a multidisciplinary team, which assesses the need or not for immunomodulatory treatment [142].

10. CURRENT REGULATORY SITUATION OF DRUGS FOR PATIENTS WITH COVID-19 IN SPAIN

Remdesivir is currently the only specific drug against COVID-19 approved by the AEMPS. It is indicated for treatment in adults and adolescents with pneumonia requiring supplemental oxygen [143].

Secondly, dexamethasone is another drug widely used in the treatment of COVID-19 and fully available in Spain [144].

The use of immunomodulators has become widespread, especially in patients at higher risk of poor outcome and in the inflammatory phase of the disease. The drugs used are approved for marketing in Spain, but in entities other than COVID-19. The most widely used are tocilizumab, authorized for the treatment of rheumatoid arthritis and cytokine release syndrome associated with treatment with CART (immunocellular therapy); Anakinra, authorized in rheumatoid arthritis, cryopyrin-associated syndromes, familial Mediterranean fever and Still's disease; and baricitinib, authorized in rheumatoid arthritis, moderate to severe, and atopic dermatitis. Regarding monoclonal antibodies, sotrovimab and the combination of casirivimab and imdevimab can be prescribed in our country for off-label indications. The European Medicines Agency (EMA) concluded that these monoclonal antibodies can be used to treat confirmed COVID-19 in adults and adolescents (aged 12 years or older and weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe COVID-19 [145,146].

The European Commission has granted marketing authorization for Ronapreve® (casirivimab and imdevimab) for the treatment of COVID-19 in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of worsening their disease, as well as for the prevention of COVID-19 in people aged 12 years and older and weighing at least 40 kg (pre- or post-exposure prophylaxis). This decision comes one day after the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), demonstrating the priority of the EMA and the European Commission to reduce review times for safe, effective

and high quality therapies in the context of the public health emergency that is COVID-19 [145, 146].

Finally, the EMA's Committee for Human Medicinal Products (CHMP) has recently begun a review of the oral antiviral drug molnupiravir (also known as MK 4482 or Lagevrio). By reviewing data as they become available, the CHMP may issue an opinion on the drug's premarketing authorization.

CONCLUSIONS

1.- Remdesivir, molnupiravir and PF-07321332 (Paxlovid) are three antivirals with different mechanisms of action that have demonstrated efficacy in clinical trials in different markers of disease progression.

2.- At present, and after many published data, convalescent plasma cannot be considered a therapy of established efficacy in patients with COVID in any of their clinical situations.

3.- There are monoclonal antibodies, both marketed and in the process of being marketed, which, when administered early in the natural course of the disease, decrease progression to severe forms.

4.- Some monoclonal antibodies under investigation could, if their efficacy is demonstrated, be administered preventively and with long-term action.

5.- The role of dexamethasone in severe patients with COVID-19 is well established. The alternative position of other corticosteroids in equivalent doses is less clear. There is no indication for administration of dexamethasone in less severe situations.

6.- There are other immunomodulatory drugs with different targets of action that already have indications in patients with severe pneumonia and respiratory failure.

7.- Of the drugs already known with other indications, fluvoxamine seems especially promising in the treatment of COVID-19.

8.- Hydroxychloroquine, azithromycin, and the anti-HIV combination of lopinavir and ritonavir have been shown to be ineffective in different studies and have no place in the current treatment of COVID-19.

9.- Studies on efficacy, safety and tolerance in pregnant women and children of any of the above drugs are limited.

10.- At the time of writing, only remdesivir is approved in Spain by the AEMPS, in the antiviral group. Some monoclonal antibodies are available on a compassionate use basis and immune response modifiers are available off-label.

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. European Medicines Agency. Comirnaty COVID-19 vaccine: EMA recommends approval for children aged 5 to 11. Accessed 26 november 2021 https://wwwemaeuropaeu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11.
2. Lin HXJ, Cho S, Meyyur Aravamudan V, Sanda HY, Palraj R, Molton JS, et al. Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence. Infection. 2021;49(3):401-10. doi: 10.1016/j.bbrc.2020.11.043 7836944.
3. Santoro MG, Carafoli E. Remdesivir: From Ebola to COVID-19. Biochem Biophys Res Commun. 2021;538:145-50. doi: 10.2147/dddt.S261154 7425093.
4. Porter DP, Weidner JM, Gomba L, Bannister R, Blair C, Jordan R, et al. Remdesivir (GS-5734) Is Efficacious in Cynomolgus Macaques Infected With Marburg Virus. J Infect Dis. 2020 Nov 9;222(11):1894-1901. doi: 10.1093/infdis/jiaa290
5. Lai CC, Chen CH, Wang CY, Chen KH, Wang YH, Hsueh PR. Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2021;76(8):1962-8. doi: 10.1093/jac/dkab093
6. Abd-Elsalam S, Ahmed OA, Mansour NO, Abdelaziz DH, Salama M, Fouad MHA, et al. Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial. Am J Trop Med Hyg. 2021. doi:10.4269/ajtmh.21-0606 .
7. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, Kåsine T, Lund-Johansen F, Hoel H, et al. Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 : A Randomized Trial. Ann Intern Med. 2021. doi:10.7326/m21-0653
8. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama. 2020. doi:10.1001/jama.2020.16349.
9. Wang Y, Zhou F, Zhang D, Zhao J, Du R, Hu Y, et al. Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. Trials. 2020;21(1):422. doi:10.1186/s13063-020-04352-9 PMC7245636.
10. Sodani P, Mucci L, Girolimetti R, Tedesco S, Monaco F, Campanozzi D, et al. Successful recovery from COVID-19 pneumonia after receiving baricitinib, tocilizumab, and remdesivir. A case report: Review of treatments and clinical role of computed tomography analysis. Respir Med Case Rep. 2020;31:101115. doi:10.1016/j.rmcr.2020.101115 PMC7320265
11. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020. doi: 10.1001/jama.2020.6019
12. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78. doi:10.1016/s0140-6736(20)31022-9.

13. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184

14. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis. 2021. doi:10.1016/s1473-3099(21)00485-0 .

15. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-26. doi:10.1056/NEJMoa2007764

16. Garcia-Vidal C, Alonso R, Camon AM, Cardozo C, Albiach L, Agüero D, et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. J Antimicrob Chemother. 2021. doi: 10.1093/jac/dkab321

17. Paranjape N, Husain M, Priestley J, Koonjah Y, Watts C, Havlik J. Early Use of Remdesivir in Patients Hospitalized With COVID-19 Improves Clinical Outcomes: A Retrospective Observational Study. Infect Dis Clin Pract (Baltim Md). 2021;29(5):e282-e6. doi:10.1097/ipc.0000000000001023.

18. Hussain Alsayed HA, Saheb Sharif-Askari F, Saheb Sharif-Askari N, Hussain AAS, Hamid Q, Halwani R. Early administration of remdesivir to COVID-19 patients associates with higher recovery rate and lower need for ICU admission: A retrospective cohort study. PLoS One. 2021;16(10):e0258643. doi:10.1371/journal.pone.0258643

19. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Recomendaciones SEIMC para el manejo clínico de pacientes con COVID-19. 2021. Available at: https://covid19seimcorg/wp-content/uploads/2021/06/SEIMC-Recomendaciones-COVID_14-05-2021pdf..

20. Infectious Disease Society of America. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. 2021. Available at: https://wwwidsocietyorg/practice-guideline/covid-19-guideline-treatment-and-management.

21. Hill JA, Paredes R, Vaca C, BJ W, Perez G, Oguchi G, et al., editors. Remdesivir for the Treatment of High-Risk Non-Hospitalized Individuals With COVID-19: A Randomized, Double-Blind, Placebo-Controlled Triale. Breaker Abstracts: COVID-19 Treatment and Prophylaxis. ID Week 2021; 2021; USA: IDSA.

22. Suzuki M, Imai T, Sakurai A, Komoto S, Ide T, Lim CK, et al. Virological and genomic analysis of SARS-CoV-2 from a favipiravir clinical trial cohort. J Infect Chemother. 2021;27(9):1350-6. doi:10.1016/j.jiac.2021.06.010

23. Dabbous HM, El-Sayed MH, El Assal G, Elghazaly H, Ebeid FFS, Sherief AF, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. Sci Rep. 2021;11(1):7282. doi:10.1038/s41598-021-85227-0.

24. Solaymani-Dodaran M, Ghanei M, Bagheri M, Qazvini A, Vahedi E, Hassan Saadat S, et al. Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia. Int Immunopharmacol. 2021;95:107522. doi:10.1016/j.intimp.2021.107522

25. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis. 2021;102:538-43. doi: 10.1016/j.ijid.2020.11.008

26. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021;157:105631. doi:10.1016/j.ejps.2020.105631

27. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021;103:62-71. doi:10.1016/j.ijid.2020.11.142

28. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8. doi:10.1016/j.ijid.2020.10.069

29. Brown LK, Freemantle N, Breuer J, Dehbi HM, Chowdhury K, Jones G, et al. Early antiviral treatment in outpatients with COVID-19 (FLARE): a structured summary of a study protocol for a randomised controlled trial. Trials. 2021;22(1):193. doi:10.1186/s13063-021-05139-2

30. Imran M, Kumar Arora M, Asdaq SMB, Khan SA, Alaqel SI, Alshammari MK, et al. Discovery, Development, and Patent Trends on Molnupiravir: A Prospective Oral Treatment for COVID-19. Molecules. 2021;26(19). doi:10.3390/molecules26195795

31. Fischer W, Eron JJ, Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. Molnupiravir, an Oral Antiviral Treatment for COVID-19. medRxiv. 2021. doi:10.1101/2021.06.17.21258639

32. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab Syndr. 2021;15(6):102329. doi:10.1016/j.dsx.2021.102329

33. Willyard C. How antiviral pill molnupiravir shot ahead in the COVID drug hunt. Nature. 2021. doi:10.1038/d41586-021-02783-1.

34. Mahase E. Covid-19: UK becomes first country to authorise antiviral molnupiravir. Bmj. 2021;375:n2697. doi:10.1136/bmj.n2697.

35. Abdelnabi R, Foo CS, Kaptein SJF, Zhang X, Do TND, Langendries L, et al. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. EBioMedicine. 2021;72:103595. doi: 10.1016/j.ebiom.2021.103595.

36. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut N, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrob Agents Chemother. 2021;65(5). doi:10.1128/aac.02428-20

37. Holman W, Holman W, McIntosh S, Painter W, Painter G, Bush J, et al. Accelerated first-in-human clinical trial of EIDD-2801/MK-4482 (molnupiravir), a ribonucleoside analog with potent antiviral activity against SARS-CoV-2. Trials. 2021;22(1):561. doi: 10.1186/s13063-021-05538-5.

38. Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagen-

esis. Nat Struct Mol Biol. 2021;28(9):740-6. doi:10.1038/s41594-021-00651-0.

39. Ahlqvist GP, McGeough CP, Senanayake C, Armstrong JD, Yadaw A, Roy S, et al. Progress Toward a Large-Scale Synthesis of Molnupiravir (MK-4482, EIDD-2801) from Cytidine. ACS Omega. 2021;6(15):10396-402. doi:10.1021/acsomega.1c00772

40. Zhao Y, Fang C, Zhang Q, Zhang R, Zhao X, Duan Y, et al. Crystal structure of SARS-CoV-2 main protease in complex with protease inhibitor PF-07321332. Protein Cell. 2021 Oct 22;1-5. doi: 10.1007/s13238-021-00883-2

41. Owen DR, Allerton CMN, Anderson AS, Aschenbrenner L, Avery M, Berritt S, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science. 2021:eabl4784. doi:10.1126/science.abl4784.

42. Pfizer. Pfzer's Novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of phase EPIC-HR Study. Nota de prensa. 2021;Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate.

43. Zuo Z, Wu T, Pan L, Zuo C, Hu Y, Luo X, et al. Modalities and Mechanisms of Treatment for Coronavirus Disease 2019. Front Pharmacol. 2020;11:583914. doi:10.3389/fphar.2020.583914.

44. Katz LM. (A Little) Clarity on Convalescent Plasma for Covid-19. N Engl J Med. 2021;384(7):666-8. doi: 10.1056/NEJMe2035678.

45. Cao H, Ming L, Chen L, Zhu X, Shi Y. The Effectiveness of Convalescent Plasma for the Treatment of Novel Corona Virus Disease 2019: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8:641429. doi:10.3389/fmed.2021.641429.

46. Aviani JK, Halim D, Soeroto AY, Achmad TH, Djuwantono T. Current views on the potentials of convalescent plasma therapy (CPT) as Coronavirus disease 2019 (COVID-19) treatment: A systematic review and meta-analysis based on recent studies and previous respiratory pandemics. Rev Med Virol. 2021. doi:10.1002/rmv.2225.

47. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. Jama. 2020. doi:10.1001/jama.2020.10044 .

48. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2020. doi:10.1056/NEJMoa2031304.

49. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, Ruiz-Antorán B, Malo de Molina R, Torres F, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. J Clin Invest. 2021. doi:10.1172/jci152740 .

50. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). Bmj. 2020;371:m3939. doi:10.1136/bmj.m3939.

51. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021. doi:10.1056/NEJMoa2033700.

52. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021. doi:10.1056/NEJMoa2107934.

53. (FDA) FaDA. Emergency Use Authorization (EUA) for the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19). FDA, 2021. (consultado 3 Nov 2021).. Available at: https://wwwfdagov/media/149534/download.

54. Unión Europea de la Salud: La Comisión establece una cartera con los diez tratamientos más prometedores contra la COVID-19. 2021. Available at:https://eceuropaeu/commission/presscorner/detail/es/ip_21_5366..

55. European Medicines Agency NdP. EMA issues advice on use of sotrovimab (VIR-7831) for treating COVID-19 (accessed 3 Nov 2021). 2021. Available at: https://wwwemaeuropaeu/en/news/ema-issues-advice-use-sotrovimab-vir-7831-treating-covid-19.

56. An EUA for Bamlanivimab-A Monoclonal Antibody for COVID-19. Jama. 2021;325(9):880-1. doi:10.1001/jama.2020.24415

57. Food and Drug Administration, release P. US Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. FDA; April 16, 2021. (accessed 10 Nov 2021). . Available at: https://wwwfdagov/media/147629/download.

58. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021. doi:10.1056/NEJMoa2102685.

59. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2021;384(3):229-37. doi:10.1056/NEJMoa2029849

60. Euroepan Medicines Agency. Questions and answers on end of rolling review for antibodies bamlanivimab and etesevimab for COVID-19 [Internet]. EMA; November 2, 2021. Bamlanivimab and etesevimab for COVID-19: Withdrawal from the rolling review process. (Consultado el 10 Nov 2021). Available at: https://wwwemaeuropaeu/en/documents/medicine-qa/questions-answers-end-rolling-review-antibodies-bamlanivimab-etesevimab-covid-19_enpdf.

61. Anonymous. An EUA for casirivimab and imdevimab for COVID-19. Med Lett Drugs Ther. 2020;62(1614):201-2. PMID: 33451174

62. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. November 21, 2020. Available at: https://bitly/2IhDxP5 Accessed June 10, 2021. 2020.

63. FDA News Release. Coronavirus (COVID-19) update: May 21, 2021. Available at: https://bitly/3fFoEUB Accessed June 10, 2021. 2021.

64. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of casirivimab and imdevimab.. Available at: https://bitly/36NmbDm Accessed: June 10, 2021.

65. Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and hu-

man studies. Cell. 2021;184(15):3949-61.e11. doi: 10.1016/j.cell.2021.06.002

66. FDA News Release. Coronavirus (COVID-19) update: June 4, 2021. . Available at: https://wwwfdagov/news-events/press-announcements/coronavirus-covid-19-update-june-4-2021 Accessed: June 10, 2021. 2021.
67. Mayer C, VanHise K, Caskey R, Naqvi M, Burwick RM. Monoclonal Antibodies Casirivimab and Imdevimab in Pregnancy for Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2021. doi:10.1097/aog.0000000000004603
68. Release FN. Coronavirus (COVID-19) update: May 21. Available at: https://bitly/3fFoEUB, 2021 Accessed: August 5, 2021. 2021.
69. Anonymous. Casirivimab and imdevimab (REGEN-COV) for post-exposure prophylaxis of COVID-19. Med Lett Drugs Ther. 2021;63(1631):130-1. PMID: 34544100
70. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med. 2021. doi:10.1056/NEJMoa2109682
71. Dong J, Zost SJ, Greaney AJ, Starr TN, Dingens AS, Chen EC, et al. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. Nat Microbiol. 2021;6(10):1233-44. doi:10.1038/s41564-021-00972-2.
72. Clinical Trials gov. Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Post-exposure Prophylaxis of COVID-19. Accessed: https://fdaaatrialstrackernet/trial/NCT04625972/. 2021.
73. Evering T, Giganti M, Chew KW, Hughes M, Moser C, Wohl DA, et al., editors. LB2 - Safety and Efficacy of Combination SARS-CoV-2 Monoclonal Neutralizing Antibodies (mAb) BRII-196 and BRII-198 in Non-Hospitalized COVID-19 Patients. IDWeek; 2021; USA.
74. Munch MW, Myatra SN, Vijayaraghavan BKT, Saseedharan S, Benfield T, Wahlin RR, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. Jama. 2021. doi:10.1001/jama.2021.18295 .
75. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. Jama. 2020. doi:10.1001/jama.2020.17022.
76. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. Jama. 2020. doi:10.1001/jama.2020.16761.
77. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. Clin Infect Dis. 2021;72(9):e373-e81. doi:10.1093/cid/ciaa1177 PMC7454320.
78. RECOVERY Collaborative Group HP, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ,. Dexamethasone in Hospitalized Patients with Covid-19. . N Engl J Med 2021;384:693-704. 10.1056/NEJMoa2021436.
79. Ye Z, Wang Y, Colunga-Lozano LE, Prasad M, Tangamornsuksan W, Rochwerg B, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. Cmaj. 2020. doi:10.1503/cmaj.200645.
80. Khaw CR, Richardson C, Bhowmik A, Agbetile J, Rajakulasingam RK. Use of Corticosteroid in Persistent Post-COVID 19 Interstitial Lung Disease. Ann Am Thorac Soc. 2021. doi:10.1513/AnnalsATS.202105-623LE.
81. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021. doi:10.1056/NEJMoa2028700.
82. Stone JH. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Reply. N Engl J Med. 2021. doi:10.1056/NEJMc2100217.
83. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020. doi: 10.1056/NEJMoa2028836.
84. Stone JH, Horick NK, Healy BC. Tocilizumab in Covid-19. Reply. N Engl J Med. 2020;384(1). doi: 10.1056/NEJMc2032911.
85. Stone JH, Horick NK, Healy BC. Tocilizumab in Covid-19. Reply. N Engl J Med. 2021;384(1):87. doi:10.1056/NEJMc2032911.
86. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;384(1):20-30. doi:10.1056/NEJMoa2030340
87. Salama C, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Reply. N Engl J Med. 2021. doi:10.1056/NEJMc2100217.
88. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021. doi:10.1056/NEJMoa2100433.
89. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10274):605-12. doi: 10.1016/s0140-6736(21)00149-5
90. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020. doi:10.1073/pnas.2005615117.
91. Martínez-Sanz J, Muriel A, Ron R, Herrera S, Pérez-Molina JA, Moreno S, et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: A multicenter cohort study. Clin Microbiol Infect. 2020. doi:10.1016/j.cmi.2020.09.021.
92. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807. doi:10.1056/NEJMoa2031994

93. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021. doi:10.1056/NEJMoa2101643

94. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021. doi: 10.1016/s2213-2600(21)00331-3.

95. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-2. doi:10.1016/s1473-3099(20)30132-8.

96. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325-e31. doi: 10.1016/s2665-9913(20)30127-2

97. Cauchois R, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A. 2020;117(32):18951-3. doi:10.1073/pnas.2009017117

98. Kyriazopoulou E, Huet T, Cavalli G, Gori A, Kyprianou M, Pickkers P, et al. Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. Lancet Rheumatol. 2021;3(10):e690-e7. doi:10.1016/s2665-9913(21)00216-2.

99. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med. 2021;27(10):1752-60. doi:10.1038/s41591-021-01499-z .

100. Coronavirus disease 19 (COVID19). Straight to the point of care. Emerging treatments. BMJ Best Practice Accessed: https://bestpracticebmjcom/topics/en-gb/3000201/emergingtxs. 2021.

101. World Health Organization. Therapeutics and COVID-19: living guideline. Accessed: https://wwwwhoint/publications/i/item/WHO-2019-nCoV-therapeutics-20213. 2021.

102. Temple C, Hoang R, Hendrickson RG. Toxic Effects from Ivermectin Use Associated with Prevention and Treatment of Covid-19. N Engl J Med. 2021. doi:10.1056/NEJMc2114907.

103. Dyer O. Covid-19: Hospital may cease giving patient ivermectin, US court rules, as prescriptions soar. Bmj. 2021;374:n2228. doi:10.1136/bmj.n2228.

104. Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis. 2021;21(1):635. doi:10.1186/s12879-021-06348-5.

105. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Respir Med. 2021 Dec;9(12):1419-1426. doi: 10.1016/S2213-2600(21)00435-5.

106. Centre for Evidence-Based Medicine, Ferner RE, Sofat R, JK. A. Drug vignettes: colchicine. 2021. Accessed: https://wwwcebmnet/covid-19/colchicine/..

107. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Accessed: https://wwwcovid19treatmentguidelinesnihgov/.

108. Stroehlein JK, Wallqvist J, Iannizzi C, Cochrane Database Syst. Rev. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst Rev 2021 May 24;(5):CD015043. doi: 10.1002/14651858.CD015043.

109. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol. 2020;203:105751. doi:10.1016/j.jsbmb.2020.105751.

110. Ibrahim S, Lowe JR, Bramante CT, Shah S, Klatt NR, Sherwood N, et al. Metformin and Covid-19: Focused Review of Mechanisms and Current Literature Suggesting Benefit. Front Endocrinol (Lausanne). 2021;12:587801. doi:10.3389/fendo.2021.587801.

111. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol. 2021;93(2):695-7. doi:10.1002/jmv.26498.

112. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2021. doi:10.1016/s2214-109x(21)00448-4.

113. World health Organization. "Solidarity" clinical trial for COVID-19 treatments: Update on hydroxychloroquine [consultado 9 de julio de 2020]. Accessed: https://wwwwhoint/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinicaltrial-

114. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020. doi:10.1056/NEJMoa2022926.

115. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. Eur J Clin Pharmacol. 2012;68(5):479-503. doi:10.1007/s00228-011-1161-x .

116. Min JY, Jang YJ. Macrolide therapy in respiratory viral infections. Mediators Inflamm. 2012;2012:649570. doi:10.1155/2012/649570.

117. Lee N, Wong CK, Chan MCW, Yeung ESL, Tam WWS, Tsang OTY, et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: A randomized controlled trial. Antiviral Res. 2017;144:48-56. doi:10.1016/j.antiviral.2017.05.008.

118. Kawamura K, Ichikado K, Takaki M, Eguchi Y, Anan K, Suga M. Adjunctive therapy with azithromycin for moderate and severe acute respiratory distress syndrome: a retrospective, propensity score-matching analysis of prospectively collected data at a single center. Int J Antimicrob Agents. 2018;51(6):918-24. doi:10.1016/j.ijantimicag.2018.02.009.

119. Mangkuliguna G, Glenardi, Natalia, Pramono LA. Efficacy and Safety of Azithromycin for the Treatment of COVID-19: A Systematic Review and Meta-analysis. Tuberc Respir Dis (Seoul). 2021;84(4):299-316. doi:10.4046/trd.2021.0075

120. Alhumaid S, Mutair AA, Alawi ZA, Alhmeed N, Zaidi ARZ, Tobaiqy M. Efficacy and Safety of Lopinavir/Ritonavir for Treatment of COVID-19: A Systematic Review and Meta-Analysis. Trop Med Infect Dis. 2020;5(4). doi:10.3390/tropicalmed5040180 .

121. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis. 2015;212(12):1904-13. doi:10.1093/infdis/jiv392.

122. World Health Organization. Women of reproductive age (15-46 years) population. . Available at: https//wwwwhoint/data/maternal-newborn-child-adolescent/indicator-explorer-new/mca/women-of--reproductive-age (15-49-years)-population-(thousands) Accessed: 20 April 2020. 2020.

123. Ko JY, DeSisto CL, Simeone RM, Ellington S, Galang RR, Oduyebo T, et al. Adverse Pregnancy Outcomes, Maternal Complications, and Severe Illness Among US Delivery Hospitalizations With and Without a Coronavirus Disease 2019 (COVID-19) Diagnosis. Clin Infect Dis. 2021;73(Suppl 1):S24-s31. doi:10.1093/cid/ciab344

124. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(44):1635-40. doi:10.15585/mmwr.mm6944e2

125. Sociedad Española de Obstetricia y Ginecología. Actualización documento técnico. Manejo de la mujer embarazada y el recién nacido con COVID_19. Version 17 junio 2020, pag 1-32. Accessed: https://segoes/infoCovid-19.

126. Pastick KA, Nicol MR, Smyth E, Zash R, Boulware DR, Rajasingham R, et al. A Systematic Review of Treatment and Outcomes of Pregnant Women With COVID-19-A Call for Clinical Trials. Open Forum Infect Dis. 2020;7(9):ofaa350. doi:10.1093/ofid/ofaa350

127. Martínez-Sánchez N, De la Calle Fernández-Miranda M, Bartha JL. Safety profile of treatments administered in COVID 19 infection in pregnant women. Clin Invest Ginecol Obstet. 2021;48(3):100663. doi:10.1016/j.gine.2021.01.004

128. Pattanashetti L, Patil S, Nyamgouda S, Bhagiratha M, Gadad P. COVID-19 and pregnant women. An overview on diagnosis, treatment approach with limitation, and clinical management. Monaldi Arch Chest Dis. 2021;91(3). doi:10.4081/monaldi.2021.1785.

129. Centers for Disease Control and Prevention. Covid-19: information for pediatric healthcare providers.2020. . Available at: https://wwwcdcgov/coronavirus/2019-ncov/hcp/pediatric-hcphtml Accessed: March26,2021. 2020.

130. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020. doi: 10.1542/peds.2020-0702

131. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. Jama. 2020. doi:10.1001/jama.2020.4344.

132. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. Bmj. 2020;370:m3249. doi: 10.1136/bmj.m3249.

133. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174(9):868-73. doi:10.1001/jamapediatrics.2020.1948

134. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-61. doi:10.1016/s2352-4642(20)30177-2

135. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatr. 2020. doi:10.1001/jamapediatrics.2020.1346.

136. de Rojas T, Pérez-Martínez A, Cela E, Baragaño M, Galán V, Mata C, et al. COVID-19 infection in children and adolescents with cancer in Madrid. Pediatr Blood Cancer. 2020;67(7):e28397. doi:10.1002/pbc.28397

137. Centers for disease Control and Prevention. Information for health providers about multisystem inflammatory syndrome in children (MIS-C). 2021 . Available at: https://wwwcdcgov/mi-c/hcp/ Accessed: March 26, 2021.

138. Carlin RF, Fischer AM, Pitkowsky Z, Abel D, Sewell TB, Landau EG, et al. Discriminating Multisystem Inflammatory Syndrome in Children Requiring Treatment from Common Febrile Conditions in Outpatient Settings. J Pediatr. 2021;229:26-32.e2. doi:10.1016/j.jpeds.2020.10.013

139. National Institutes of Health, Covid-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID 19). Treatment Guidelines. Accessed:https://wwcovid19 treatmentguidelines nihgov/11/12/2021. 2021.

140. Food and Drug Administration. Fact sheet for healthcare providers : emergency use authorization (EUA) of veklury (remdesivir) for hospitalized pediatric patients weighing 3.5kg to less than 40kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5kg. 2020- Accessed: https://wwwfdagov/media/1375667. 2020.

141. Wolf J, Abzug MJ, Wattier RL, Sue PK, Vora SB, Zachariah P, et al. Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents. J Pediatric Infect Dis Soc. 2021;10(5):629-34. doi:10.1093/jpids/piaa175

142. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children. Jama. 2021. doi: 10.1001/jama.2021.0694.

143. Ficha técnica. Veklury 100 mg concentrado para solución para per-

fusión. Consultado el 1 de Noviembre de 2021. Accessed: https://cimaaempses/cima/dochtml/ft/1201459001/FT_1201459001html). 2020.

144. Sarzani R, Spannella F, Giulietti F, Di Pentima C, Giordano P, Giacometti A. Possible harm from glucocorticoid drugs misuse in the early phase of SARS-CoV-2 infection: a narrative review of the evidence. Intern Emerg Med. 2021:1-10. doi: 10.1007/s11739-021-02860-3

145. European Medicines Agency. EMA issues advice on use of sotrovimab (VIR-7831) for treating COVID-19. Accessed: https://wwwemaeuropaeu/en/news/ema-issues-advice-use-sotrovimab-vir-7831-treating-covid-19; 2021. November 1, 2021

146. European Medicines Agency. EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab).2021. Accessed: https://wwwemaeuropaeu/en/news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimab-imdevimab).

Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
doi:10.37201/req/083.2021

Past and future of HIV infection. A document based on expert opinion

Emilio Bouza[1]
José Ramón Arribas[2]
Belén Alejos[3]
José Ignacio Bernardino[4]
Maye Coiras[5]
Pep Coll[6]
Jorge Del Romero[7]
María José Fuster[8]
Miguel Górgolas[9]
Alipio Gutiérrez[10]
Diego Gracia[11]
Victoria Hernando[12]
Javier Martínez-Picado[13]
José Manuel Martínez Sesmero[14]
Esteban Martínez[15]
Santiago Moreno[16]
Beatriz Mothe[17]
Maria Luisa Navarro[18]
Daniel Podzamczer[19]
Federico Pulido[20]
José Tomás Ramos[21]
Ezequiel Ruiz-Mateos[22]
Inés Suárez García[23]
Esteban Palomo[24]

[1]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Department of Medicine, Universidad Complutense de Madrid (UCM), Instituto de Investigación Sanitaria Gregorio Marañón, and CIBER de Enfermedades Respiratorias (CIBERES CB06/06/0058), Madrid.
[2]Director of HIV and Infectious Diseases Research, Hospital La Paz. Madrid. Associate Professor at the Universidad Autónoma de Madrid.
[3]Researcher at the Instituto de Salud Carlos III. Madrid
[4]HIV Unit. Internal Medicine Department. La Paz Hospital
[5]AIDS Immunopathology Unit. National Microbiology Centre. Carlos III Healthcare Institute, Madrid.
[6]IrsiCaixa-Institut de Recerca de la Sida. HIV Unit. Germans Trias i Pujol Hospital. Badalona. BCN Checkpoint. Barcelona.
[7]Director of the Sandoval Health Centre. IdISSC. San Carlos Clinical Hospital. Madrid
[8]Executive Director of the Spanish Interdisciplinary AIDS Society (SEISIDA) and Professor at the UNED. Madrid.
[9]Associate Head of Infectious Diseases. Jiménez Díaz Foundation. Madrid
[10]Head of Health Content at RTVM and 1st vice-president of the ANIS National Association of Health Informers. Madrid.
[11]President of the Health Sciences Foundation. Madrid
[12]National Epidemiology Centre-Carlos III Health Institute. Madrid
[13]Research Professor at the Catalan Institute for Research and Advanced Studies (ICREA) at IrsiCaixa and Associate Professor at the University of Vic (UVic).
[14]Head of the Pharmacy Department, San Carlos Clinical Hospital, Madrid.
[15]Senior Consultant, Infection Service, Clinical Hospital, Barcelona
[16]Department of Infectious Diseases, Ramón y Cajal University Hospital, Department of Medicine and Medical Specialities, University of Alcalá (UAH), Ramón y Cajal Institute of Health Research, and AIDS Research Network, Madrid.
[17]IrsiCaixa - Institut de Recerca de la Sida, Infectious Diseases Service, Hospital Germans Trias i Pujol, Badalona.
[18]Group Infections in the Paediatric Population. Paediatric Infectious Diseases Section. Gregorio Marañón General University Hospital. Madrid.
[19]HIV and STI Unit, Infectious Diseases Department. Hospital Universitari de Bellvitge. Barcelona.
[20]Assistant Doctor at the HIV Unit of the Hospital Universitario 12 October, imas12, Madrid. Associate Professor at the Complutense University of Madrid.
[21]Head of the Paediatrics Department, UCM Professor of Paediatrics. San Carlos Clinical Hospital, Madrid.
[22]Clinical Unit for Infectious Diseases Virgen del Rocío University Hospital / Seville Institute de Biomedicine. Seville. / CSIC/ Seville University.
[23]Infanta Sofía University Hospital, Madrid. Universidad Europea, Madrid.
[24]Doctor in Pharmacy. Health Sciences Foundation Director. Madrid.

Article history
Received:16 June 2021; Accepted: 2 September 2021; Published: 12 January 2021

ABSTRACT

HIV infection is now almost 40 years old. In this time, along with the catastrophe and tragedy that it has entailed, it has also represented the capacity of modern society to take on a challenge of this magnitude and to transform an almost uniformly lethal disease into a chronic illness, compatible with a practically normal personal and relationship life. This anniversary seemed an ideal moment to pause and reflect on the future of HIV infection, the challenges that remain to be addressed and the prospects for the immediate future. This reflection has to go beyond merely technical approaches, by specialized professionals, to also address social and ethical aspects. For this reason, the Health Sciences Foundation convened a group of experts in different aspects of this disease to discuss a series of questions that seemed pertinent to all those present. Each question was presented by one of the participants and discussed by the group. The document we offer is the result of this reflection.

Keywords: HIV infection, AIDS, chronic disease, history, prevention, epidemiology, eradication, vaccine, two-drug treatment, immunotherapy.

Pasado y futuro de la infección por VIH. Un documento basado en la opinión de expertos

RESUMEN

La infección por VIH cumple ahora casi 40 años de existencia. En este tiempo, junto a la catástrofe y la tragedia que ha supuesto, ha representado también la capacidad de la sociedad

Correspondence:
Emilio Bouza MD, PhD.
Gregorio Marañón Health Research Institute.
C/ Dr. Esquerdo, 46
28007 Madrid, Spain
E-mail: emilio.bouza@gmail.com

moderna de asumir un reto de esta magnitud y de transformar, gracias al tratamiento antirretroviral, una enfermedad mayoritariamente letal en una enfermedad crónica, compatible con una vida personal y de relación prácticamente normales. Este aniversario parecía un momento idóneo para pararse a reflexionar sobre el futuro de la infección VIH, los retos que todavía quedan por abordar y las perspectivas para el inmediato futuro. Esa reflexión tiene que ir más allá de planteamientos meramente técnicos, de profesionales especializados, para abordar aspectos sociales y éticos. Por este motivo, la Fundación de Ciencias de la Salud convocó a un grupo de expertos en distintos aspectos de esta infección para discutir una serie de preguntas que parecieron pertinentes a todos los convocados. Cada pregunta era expuesta por uno de los participantes y discutida por el grupo. El documento que ofrecemos es el resultado de esa reflexión.

Palabras clave: Infección VIH, SIDA, enfermedad crónica, historia, prevención, epidemiología, erradicación, vacuna, tratamiento con dos fármacos, inmunoterapia

INTRODUCTION

The AIDS epidemic is now 40 years old. While it is one of humanity's greatest tragedies, it is at the same time one of its greatest successes in scientific development and research. What was achieved was unimaginable 4 decades ago: to turn a profoundly immunosuppressive disease into a chronic infection where a latent virus allows, under very tolerable medication, a state almost close to normality. The research effort has been enormous, but the results are extraordinary.

On the other hand, the failure to eradicate the disease, the failure to produce a vaccine and the problems of social injustice that still persist around HIV infection still leave room for improvement.

It therefore seems appropriate to undertake a process of reflection on where we are after almost four decades and where we want to be in the not-too-distant future. This reflection can only be complete if it is carried out from a multidisciplinary perspective that includes the points of view of the different actors involved in the problem.

For this reason, the Health Sciences Foundation convened a large group of people from different backgrounds to try to provide answers to a series of questions that society is asking about the past and future of HIV infection. The questions posed were accepted by the group as relevant and assigned to a speaker who presented his or her point of view and data for discussion with the group.

We now turn to the questions, the rationale underpinning the answer and the conclusions on each point.

AS WE APPROACH THE 40TH ANNIVERSARY OF THE BEGINNING OF THE HIV EPIDEMIC, WHAT MAJOR HISTORICAL MILESTONES WOULD YOU HIGHLIGHT?

Daniel Podzamczer

There are probably many milestones in the history of HIV infection since its discovery, but I would highlight the following 12:

1. On June 5th, **1981**, the CDC alerted of the occurrence of 5 cases of **Pneumocystis carinii** (now *P. jirovecii*) **pneumonia** in previously healthy homosexual men, associated with CMV disease or infection and suggesting that it was due to an immunodeficiency whose cause was not yet known [1-4].
2. In **1984,** French researchers on the one hand and US researchers on the other - with controversy over the claim to first discovery - isolated a virus they called **HTLVIII (US) or LAV (France)**, later unified as HIV, as the cause of the so-called acquired immunodeficiency syndrome **(AIDS)**. This landmark finding made it possible,months later, to detect the presence of antibodies to the virus through **serological tests** that were immediately widely used to diagnose HIV infection in people who had contracted the virus [5-13].
3. In the **1980s**, the knowledge that **famous personalities** from the world of art and sport (Rock Hudson, Freddy Mercury, Magic Johnson, etc.) had been infected with HIV was important in drawing attention to a growing pandemic and demonstrating that it did not only affect marginalised groups in society [14].
4. In **1987**, the first antiretroviral drug, **AZT** (azidothymidine or zidovudine), was marketed in Spain, with the capacity to partially and temporarily inhibit HIV replication, demonstrating in a randomised, double-blind clinical trial that patients receiving this treatment had a significantly longer survival (although the difference was only months). AZT also had considerable toxicity, but it was the first therapeutic step in the fight against HIV [14, 15].
5. In **1994**, study 076 was the first to demonstrate that effective antiretroviral treatment (ART) was able to **prevent vertical transmission of HIV in pregnant women**. This randomised, double-blind clinical trial showed a 76% reduction of infection in newborns of women taking AZT during pregnancy versus placebo[16].
6. In **1996**, coinciding with the International AIDS Conference in Vancouver, it was shown that a **three-drug** regimen of **ART** - two nucleoside analogues and a protease inhibitor - was able to persistently inhibit HIV replication and at least partially restore immunity as assessed by CD4 count and CD4/CD8 ratio [17].
7. That same year, we were able to start assessing the response to ART in our hospital laboratories by measuring **plasma viral load**, which allowed us to know within a few weeks whether or not the treatment was being effective[18]. **In 2005**, the first scientific evidence of the **preventive efficacy of suppressive ART on sexual transmission of HIV** in serodiscordant heterosexual couples was presented [19].
8. In **2007**, the first triple-ART regimen (TDF/FTC/EFV) was marketed in Spain in a **single tablet to be administered once a day** [20]**.** It was the beginning of a phase that was

followed in the next decade by the marketing of several one-pill-a-day formulations of effective, well-tolerated and easy-to-take drugs, some of them based on a **high genetic barrier integrase inhibitor**; drugs now considered preferred drugs for ART initiation [21]. This has contributed significantly to transforming HIV infection into a **chronic disease** with a survival similar to the general population in patients who start ART early in the course of infection - and with an excellent quality of life. The first **long-term ART** with an INI - Cabotegravir - and an NNRTI - Rilpivirine - will soon be marketed, allowing patients who are considered good candidates to receive **intramuscular injections** every 2 months instead of taking daily pills, which may have benefits on adherence, quality of life and stigma for HIV-infected people [22].

9. In **2009**, the first data were released on the so-called **"Berlin patient"**, the first HIV-infected adult to be assumed to have been cleared of the virus - and therefore **cured –** following a bone marrow transplant for treatment of leukaemia refractory to chemotherapy and radiotherapy. This transplant was from a **donor with the delta 32 mutation of the CCR5 co-receptor** of CD4 cells, which has long been known to confer immunity of CD4 cells to HIV, which is unable to infect them [23].
10. In **2011**, the HPTN052 study showed that early ART initiation in serodiscordant couples reduced HIV transmission by 96%. These data were key to the widespread recommendation for early initiation of ART regardless of CD4 count [24].
11. In **2012**, the FDA approved pre-exposure prophylaxis **(PrEP),** the administration of a daily TDF/FTC regimen to patients at high risk of HIV infection due to sexual practices. This approval was based on several international clinical trials of thousands of participants - men who have sex with men, women and heterosexual men - which showed that such treatment was able to reduce the proportion of people acquiring sexually transmitted infections by 40-86%, depending on the study, provided adherence was acceptable. The preventive benefits of PrEP, which has been shown to be cost-effective, were seen in the following years in the significant decrease in the incidence of new HIV infections in cities or countries where its use was authorised [25]. In November 2019, PrEP was approved and included in the National Health System's service portfolio.
12. Data from the PARTNER 1 and 2 studies demonstrating the **absence of sexual transmission** of HIV from ART-infected individuals with undetectable plasma viral loads were published **in 2016 and 2019**. Undoubtedly these important data (summarised in the I=I expression (undetectable=untransmissible; undetectable=untransmittable", or "U=U") can contribute to reducing the stigma and psychological problems associated with HIV infection [25-27].

Conclusion:

After 40 years, HIV infection has changed from being a fatal disease, in the vast majority of cases, to a chronic infection, with an excellent quality of life for people on antiretroviral treatment (ART). New prevention measures, the efficacy of current ART and the absence of transmission in virologically suppressed individuals will help to reduce the incidence of infection, as well as its social stigma, pending a cure.

WHAT IS THE CURRENT SITUATION OF THE EPIDEMIC IN FIGURES?

Belén Alejos

According to the latest UNAIDS report, 37.9 million people were living with HIV infection globally in 2018. Of them, 79% of people living with HIV knew their HIV status (i.e. about 8.1 million people did not know they were living with HIV). In terms of access to antiretroviral treatment, 23.3 million people had access to antiretroviral therapy, up from 7.7 million in 2010. Consequently, there has been a steady decline from the number of new infections to 1.7 million new HIV infections in 2018 [28].

In the WHO European Region, which includes Europe and Central Asia, 159,420 new diagnoses were recorded in 2017, corresponding to a rate of 20.0 new diagnoses per 100,000 people. As has been observed over the last decade, most of these cases were recorded in the eastern region (82%), followed by the western region (14%) and the central region (4%). The current HIV epidemic varies greatly by geographical area. Epidemics in the central and eastern regions account for the majority of cases, and the most frequent mode of transmission is heterosexual practices followed by injection drug use. In contrast, in the western part of Europe, sex between men was the most common mode of transmission [27]. Overall, the rate of new HIV diagnoses increased by 37% from 2008 to 2017 across the WHO European Region, but there are also different patterns by geographical area. While a 27% decrease in the rate of new diagnoses is observed in the western region, rates continue to increase in the eastern and central regions (68% and 121% respectively). In addition, diagnostic delay remains very high in all regions and more than half of new diagnoses were late presenters (CD4 < 350 cells/μL).

In Spain, it is estimated that there are currently between 140,000 and 170,000 people living with HIV, which represents a prevalence of 0.4%. According to data from the epidemiological surveillance report on HIV/AIDS in Spain, 3,381 new HIV diagnoses were recorded in 2017, giving a rate of 8.82 cases per 100,000 inhabitants after correcting for delayed reporting [29]. This rate is similar to other countries in the WHO European region, but higher than the average for EU and Western European countries. In comparison with the countries of the European Union/European Economic Area (EU/EEA), we observe in Spain a higher percentage of diagnoses in men (84.6% versus 75.1%) and a lower percentage in people over 50 years of age (14.8% versus 19.3%). The most frequent mode of transmission is men who have sex with men (54.3%), followed by heterosexual (28.2%) and injection drug users (3.1%) [30].

The time trend in the rate of new diagnoses in Spain in

the period 2009-2017 is downward, however different patterns are observed depending on the mode of transmission. In the groups of injection drug users and heterosexual practices, a steady decline is observed throughout the period for both males and females. Whilst in the group of men who have sex with men a downward trend is observed only from 2015 onwards, although disaggregated by origin this decrease is only observed in Spanish MSM. Although late diagnosis has decreased slightly since 2009, it is still very high; in 2017 47.8% of HIV diagnoses were made late (CD4 < 350 cells/µL).

The 90-90-90 targets set by UNAIDS are that by 2020 at least 90% of people living with HIV should be diagnosed; at least 90% of diagnosed people should be on antiretroviral treatment; and at least 90% of people on antiretroviral treatment should have an undetectable viral load. Overall, this would mean that at least 73% of people living with HIV have an undetectable viral load. Modelling suggests that achieving these targets by 2020 would mean ending the epidemic by 2030.

The Spanish figures on the 90-90-90 strategy have been provided by the HIV and Risk Behaviour Surveillance Unit [31]. Of the 146,500 people living with HIV in Spain, 86.2% knew their HIV diagnosis, 93.4% were receiving antiretroviral treatment, and of those on treatment, 90.4% had reached an undetectable viral load. Although we are above the EU/ EEA average and very close to achieving the targets set by UNAIDS for 2020, there are still approximately 13.7% of people living with HIV in Spain who do not know they have the infection.

Conclusion:

HIV remains a priority for European Public Health. However, we have effective tools such as universal prevention, screening and treatment to address the fight against the HIV epidemic. It is therefore essential that these tools be implemented more widely and adapted to the time and characteristics of the epidemic.

IS HIV ERADICATION POSSIBLE? FOR WHAT YEAR?

Victoria Hernando

In 2014, the United Nations Programme on HIV and AIDS (UNAIDS) set the 90-90-90 target for the year 2020, so that 90% of people living with HIV would know their diagnosis, 90% of them would receive antiretroviral treatment and 90% of people on treatment would have a suppressed viral load, aiming for the end of the AIDS epidemic by 2030 [32]. These targets are monitored through the "treatment cascade" or "continuum of care" that allows the HIV epidemic situation in a particular country or geographic area to be assessed. In Spain, in 2016, the percentages of each of these targets would be: 86.2%, 93.4% and 90.4%, so we would be very close to reaching the targets set by UNAIDS [32].

Various mathematical models have estimated that if the 90-90-90 targets proposed by UNAIDS were achieved globally, increasing levels of diagnosis and antiretroviral treatment coverage could achieve an approximate 40% reduction in annual HIV incidence globally [33]. However, it should be borne in mind that in countries such as Spain, where access to treatment is universal and the fraction undiagnosed is low, the improvement that would be achieved in reaching the UNAIDS targets on incidence reduction would not be as great as in other countries where the prevalence of HIV infection is higher [34].

To the question posed here, "Is it possible to eradicate HIV?", the answer from a public health point of view is clearly, no. When we talk about HIV eradication, we can find a clinical concept, which would be the cure of the individual, i.e. the complete eradication of the virus from a patient's body. On the other hand, eradication, as an epidemiological or public health concept, at the population level, is defined as the complete elimination of the disease-causing agent from the natural environment (not from controlled laboratories). In any case, HIV eradication is not a goal that we can set as achievable in a short period of time. In the case of complete cure of the individual, we know that even with the highly effective antiretroviral therapy available to us, and even if the subject has an undetectable viral load, there remains a low level of viral replication and cellular reservoirs that contribute to HIV persistence and make HIV infection a chronic disease [33]. To achieve eradication at the population level, curative treatment and preventive vaccines should be available and affordable for the entire world population.

We can, however, speak of elimination and control in some areas with regard to HIV infection. Disease elimination refers to the complete cessation of the incidence of cases in a given geographical area or population subgroup. For HIV infection this has been achieved for blood transfusion-associated transmission and mother-to-child transmission[35]. But unlike eradication, in the case of elimination, as the causative agent is still present in the natural environment, we must maintain the preventive and intervention measures that led to the elimination of the disease.

The primary prevention measures that allowed us to reach this level have been HIV testing of all blood donors and monitoring of pregnant women - HIV testing during pregnancy, antiretroviral treatment of pregnant HIV-infected women and newborns, and formula feeding of newborns. While there may still be cases of vertical transmission of HIV, these cases must be examined to identify where prevention systems and policies have failed to ensure universal access to prevention methods.

There are other primary prevention measures (aimed at preventing the onset of infection) that can be taken depending on the environment in which we find ourselves [33], harm reduction programmes for injecting drug users (syringe exchange, supervised consumption rooms, methadone treatment) [36], PrEP [36-38] and male circumcision in certain contexts[39]. All these measures that we can apply to reduce sexual transmission of the virus and the acquisition of infection through injection drug use are aimed at infection control, i.e. reducing the incidence, prevalence or mortality of cases in a

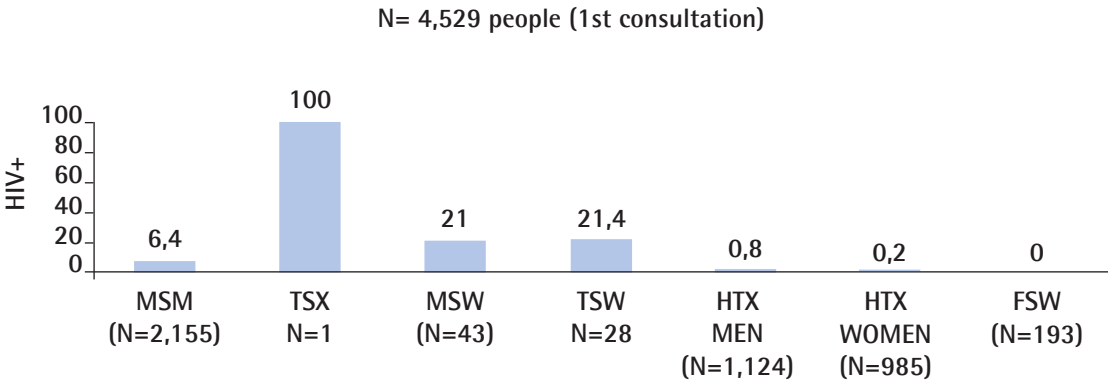


Figure 1 Sandoval Centre 2018. HIV seroprevalence at first visit, by exposure category. N= 4,529 people (1st consultation).

MSM: Men who have sex with men; TSX: Transgender people; MSW: Male sex workers, TSW: Transgender sex workers; HTX: Heterosexual; FSW: Female sex workers

given geographical area. The elimination of sexual transmission of HIV, i.e. zero incidence, cannot be considered a realistic goal, as the number of cases through this mode of transmission remains very high.

In addition, we can highlight other key aspects of monitoring the HIV epidemic that help control infection and improve the situation of people living with HIV infection. These would be secondary prevention measures such as early diagnosis and rapid access to antiretroviral treatment. Increase the frequency of HIV testing, especially for people at high risk of acquiring HIV infection, such as men who have sex with men (MSM) and people who inject drugs [40]. In recent years, HIV testing sites have diversified to include not only health care settings, but also community settings, and there is a need to promote rapid, safe and confidential access, as there is still a high burden of discrimination and stigmatisation of people with HIV infection. According to Public Health England (PHE) officials, this has been one of the key points in the decline in the numbers of new HIV diagnoses in recent years in England [41,42].

Similarly, early initiation of antiretroviral therapy not only slows disease progression in the HIV-infected person, but also helps control the onset of other co-morbidities associated with both HIV infection and the longer life expectancy of HIV-infected people. It also interrupts transmission of the virus, as a person who achieves and maintains an undetectable viral load does not transmit HIV to sexual partners [43]. High adherence to prescribed antiretroviral treatment is vital to maintain the effectiveness of this preventive measure.

Conclusion:

We cannot currently consider the eradication of HIV as an achievable goal in the near future, but we can reduce to zero the incidence of cases in certain modes of transmission and improve control in others, such as sexual transmission.

WHAT IS A PERSON AT RISK? HOW IS IT DEFINED?

Jorge del Romero

The epidemiology of HIV in the world is highly variable in each geographic region.

In Europe, HIV prevalence is 0.4%, while in Africa it is around 4% (WHO, 2018) [44]. According to WHO, the following are generally considered "specific populations" for STIs/HIV:

- Sex workers and their clients
- Men who have sex with men (MSM)
- Transgender people (TSX)
- Prison inmates
- Youths and adolescents
- Drug users

A study conducted at an STI clinic in Madrid in 2016 [45] concluded that those most at risk of HIV infection were: MSM between 20 and 39 years old, with several previous negative serologies, a history of STIs and multiple sexual partners with whom they had sex without condoms, under the effect of recreational drugs (chemsex) [46].

The highest prevalences of HIV infection observed among the 4,529 people seen for first consultations at the Sandoval Centre in 2018 were among transgender men and women in sex work (MSW, FSW) and men who have sex with men (MSM) (Figure 1)

Conclusion:

Particularly at risk of HIV infection are: sex workers and their clients, men who have sex with men, transgender people, prison inmates, young people and adolescents, and people who use drugs for sexual relations (chemsex).

The greatest risk is not knowing that you are HIV-positive or, if you do know, not being able to access antiretroviral treatment.

WHAT IS LIFE LIKE FOR AN HIV-POSITIVE PATIENT IN PHYSICAL TERMS?

Maria José Fuster

Overall, it can be stated that the clinical situation of people living with HIV (PLHIV) has evolved positively with the expansion of antiretroviral treatment and there is a continuing trend towards improvement in key clinical immunological and virological parameters [47]. However, there are different profiles of PLHIV and different levels of complexity in their health care needs. The challenges faced by older PLHIV with co-morbidities are not the same as those faced by controlled and stable patients, those who are newly diagnosed, those with problematic substance use, or those who are socially excluded, to give an example of different profiles. Therefore, the life of PLHIV in all its facets is not homogeneous but there is a lot of variability.

Recent research by the Spanish Interdisciplinary AIDS Society (SEISIDA) measuring quality of life in a large sample of PLHIV in Spain (n=1,441) showed that the overall health perception and quality of life score was close to 70 on a scale of 100 (68.5 ± 22.61). Health perception was lower in certain well-established PLHIV profiles, such as people over 50, women, or those with a lower socio-educational level[48]. The overall perception of health is influenced by many factors, one of them being the symptoms experienced on a daily basis. A study of a cohort of HIV-positive veterans in the United States showed that several of the symptoms they experienced predicted decreased quality of life, survival, and increased hospitalisations [49]. The most prevalent symptoms found in other countries with large cohorts of PLHIV are sleep problems, muscle pain, fatigue, sadness, anxiety, sexual problems, and abdominal pain/distension [50]. SEISIDA studies [51,52] show data in line with these findings, as the most prevalent symptoms in PLHIV in Spain are the same, and the most bothersome are sleep and sexual problems. The general health and symptoms experienced by PLHIV relate to many aspects of the process of living with HIV; the experiences, thoughts and emotions involved. A qualitative study that SEISIDA and the Institute for Global Health (ISGlobal) are conducting to improve the quality of life of PLHIV shows, among other findings, that sleep problems and fatigue are related to social problems prevalent in HIV, such as economic deprivation and stigma. These symptoms are also associated with the emotional distress caused by the worries and fears that PLHIV have to cope with on a daily basis, such as uncertainty about the future or fear of rejection. These or other symptoms are also related to health habits or effects of medication. Symptoms are interconnected and often lead to a "vicious cycle" as they have different possible causes, the causes may determine various symptoms and depending on them, the intervention and self-management of the symptom will be different. So where should we start? It is essential to detect these problems in order to be able to intervene and respond to them. Studies show a very high discrepancy between the symptoms reported by patients and what their doctors thought they were suffering from. The SEISIDA and ISGlobal qualitative study explored the reasons for the lack of detection and management of important symptoms and concerns of PLHIV in routine clinical practice [51] . The difficulty for the patient to define what is wrong or what he/she feels (i.e. to identify it), the lack of knowledge or solutions to the problem and the deficits in the relationship between the health professional and the patient, among other aspects, mean that no response is given to these health-related problems that can damage quality of life [53].

Conclusion:

The life of an HIV-positive patient brings with it a daily need to take responsibility and self-manage their health process, and this involves making physical, but also psychological and social adjustments that are closely related. Self-management tasks involve managing medical issues, such as taking medication, managing adverse effects or symptoms; managing behaviours, such as lifestyle and habits; and coping with emotional issues associated with HIV.

WHAT ROLE SHOULD THE MEDIA PLAY?

Alipio Gutiérrez

The first thing is to observe the maximum scientific rigor. In the same way that medicine is moving towards precision, personalised medicine, we should seek precision journalism. With rigor, with data and scientific evidence. All the more so because now the media, like citizens, also communicate through social networks and there, scientific evidence does not gain value, it is not a plus in any way. Sometimes, on the contrary, the scientific truth about any health issue, and in this case, about HIV infection, has no relevance because anyone can assert their opinion on whatever they want and even if they do not have the truth, if they have a loyal following on social media, they can make that opinion prevail over the scientific reality of the moment. This is why I believe that it is necessary to effectively design specific profiles for the media, scientific societies, patient associations and health administrations in order to know how to "compete" in this new communication scenario.

Secondly, we must fight the social stigma of those affected by HIV. For this, "MASS MEDIA" is the best and most effective tool, together with the school. It has taken decades to put a face to this disease and it is still "hidden" today. What is hidden does not exist and also prevents normalisation. We must commit to the elimination of the social stigma against people affected by HIV that affects their lives.

Thirdly, the media should bring back the visibility that this epidemic had when it was deadly. At the time, it was frequently featured in the media. Now that the disease "does not kill", and has become chronic, it is no longer news. But this makes it all the more paradoxical. I believe that this is a commitment of ours that is highly topical because we are in the "time of chronicity" and it is important that everything related to HIV, from research to the social normalisation of those affected, is

once again reflected in the different media as a reflection of what is happening in society.

Finally, I am going to say something which, being a journalist myself, may come as a shock: we have to stop being objective about health issues in general. We must be belligerent with scientific evidence, with scientific rigor and eliminate this perverse practice of journalism that, in my opinion, is not sustainable in terms of health. Some media treat health issues like any other issue, wielding an objectivity based on EQUIDISTANCE, offering the same time, the same space in a newspaper, TV or radio programme to those who hold one opinion and those who oppose it. This is NOT VALID in health. It is as if, by virtue of this objectivity/equidistance, we were to propose, for example, offering the same time and space in the media to those who defend the Universal Declaration of Human Rights and those who violate them.

With health issues, and HIV being a clear example, we have to be belligerent and always take the side of scientific evidence.

Conclusion:

In its relation to HIV disease, the media must remain topical, adhere to scientific objectivity, help to overcome the social stigma of those affected and contribute to the physical and psychological well-being of those affected.

HAVE WE ENDED VERTICAL TRANSMISSION?

Jose Tomás Ramos

Vertical transmission (VT) is the predominant mode of HIV-1 transmission in children and is the route of infection for the vast majority of new infections worldwide. In natural history, VT ranges from 15-25% in the absence of breastfeeding, rising to 40% in populations where breastfeeding is necessary, such as in low-income countries where the vast majority of infections occur globally [54]. Since the 1994 ACTG 076 trial, in which zidovudine was administered in pregnancy, delivery and to the neonate, documenting 67% efficacy of antiretroviral therapy (ART) in preventing VT, there have been enormous advances in the prevention of VT [16]. Viral load in pregnancy is the most important independent factor associated with VT. In developed countries, the use of combination ART and effective virological suppression to undetectable levels in pregnancy, maintained during delivery, leads to transmission rates of less than 1% [55]. Prospective follow-up of pregnant women with HIV and their children has been carried out since 2000 in 9 public hospitals in the Community of Madrid, with data from 1,475 mother-child pairs up to December 2018. Overall VT was 1.2% (95% CI: 0.7-1.8%), currently less than 0.5%. Moreover, in the few VT cases that have occurred, there were missed opportunities to avoid it [56]. When effective ART is initiated before conception and undetectable viral load is maintained until delivery, vertical transmission may be eliminated, as demonstrated by a study in France in which of 2,651 mothers who initiated ART before conception and remained with viral load < 50 copies/ml close to delivery; there was not a single transmission to the newborn (95% CI): 0.1%) [57].

In low-income countries, where breastfeeding is the main source of nutrients, VT can also be drastically reduced to rates below 2% with early detection of infection in pregnancy and continuous ART during breastfeeding to be maintained for life (WHO option B+), which would prevent infection in new pregnancies. Although progress is quite remarkable, with the number of pregnant women treated with antiretrovirals having doubled in the last decade to 92%, and the number of new infections in children having fallen by more than 70%, there were still 160,000 new infections in children by VT in 2018 [28].

The goal of VT elimination requires much more than the availability, efficacy and safety of antiretrovirals for universal lifelong treatment in women. A comprehensive approach is needed, including reducing new infections in women of childbearing age and a sequence of maternal and newborn interventions, the removal of which at any point can lead to reduced effectiveness in preventing VT. This chain of prevention includes adequate gestational control with sufficient antenatal care, HIV testing and repeat testing during pregnancy and in low-income countries also during breastfeeding, ART as early as possible for new diagnoses in pregnancy, post-exposure prophylaxis for newborns, and retention in the health system. It is precisely the most vulnerable populations that have the greatest difficulty in complying with all the Available at:s in the epidemiological chain, and in whom prevention failures are most common. These higher-risk groups include migrant populations who are diagnosed or who present late during pregnancy or childbirth, drug users or the growing population of mothers who are themselves infected by VT, in whom adherence is a challenge and selection of resistant virus more prevalent.

On the other hand, although current ART is very effective and integrase inhibitors allow for a more rapid decline in viral load during pregnancy, they are not without toxicity. Current WHO guidelines recommend dolutegravir-based regimens, which may be associated with an increased risk of neural tube defects in sub-Saharan populations. Although the benefits far outweigh the potential adverse effects, comprehensive epidemiological surveillance of all antiretrovirals is required to establish safety in the newborn and thus define the most appropriate treatment regimen in each risk situation.

Even with today's great advances, there are still high-risk cases of vertical transmission where, although it is too late to take preventive measures during pregnancy, it is still possible to intervene at birth and in the newborn with immediate combined prophylaxis. Even when there has been intrauterine infection detected by diagnosis in the first 48h, immediate ART to the newborn could allow us to prevent the spread of the virus, reduce the viral reservoir as much as possible, and perhaps a potential eradication.

Conclusion:

Elimination of vertical transmission of HIV in low-income countries is feasible. To achieve this, prevention of

HIV infection in women of childbearing age and early diagnosis to enable early and safe antiretroviral treatment for all infected women is essential.

WHAT HAPPENED TO CHILDREN BORN WITH HIV?

Marisa Navarro

HIV infection in paediatrics has undergone a huge change in recent years thanks to the combination of antiretroviral therapy (cART). CART is preventing perinatal transmission while controlling viral replication in infected children.

In Spain, since 2008 there has been a follow-up cohort of HIV-positive children and adolescents from the AIDS Research Network (CoRISpe), which includes patients treated in Paediatric Units (PU) since 1995. CoRISpe is in turn linked to the HIV Biobank of the AIDS Research Network, and is allowing us to learn about the evolution of paediatric infection in our country.

In CoRISpe, 1,344 patients are registered. Most of them were born before universal HIV screening in pregnant women, with 10% of patients in the cohort dying, mostly prior to cART.

CoRISpe is a cohort of mainly adolescent and young adult patients who survived the early years of the epidemic before cART became available, with 51% having transferred to Adult Units (AU). New CoRISpe patients are mainly immigrant children born in sub-Saharan Africa and Central and South America, with new HIV infections in children born in Spain being anecdotal.

At the end of 2017, 403 young adults with vertical transmission are being treated in the AUs. These patients have a median age of 25 (ICER 23.6-25.8) and have been followed up in UA after transition for 7.5 years (ICER 5.1-10.5). Of them, 95% were born in Spain and 56.7% are women. Clinical stage is 29.6% A, 40.4% B, 30% C. Some 95% are receiving cART, with 76% receiving once-daily (OD) regimens and 81% with HIV viral load <50 copies/ml [58]. Immune status is good, with CD4 of 723/mm3 (RIC 500-965) although 33% have a CD4/CD8 ratio below 1 [59].

Analysing the accumulated resistance mutations in a group of 133 patients transferred and compared to patients still in PU, a higher percentage of acquired resistance mutations was observed (75% vs 28% p=0.006), mainly to nucleoside analogues (67% vs 28% p<0.0001), and to protease inhibitors (32% vs 16% p=0.0384). In this substudy, despite having good immune status, 74% have >500 TCD4 cells/mm^3. Only 65% are found with suppressed viral load, reflecting the difficulties in treating these patients with extensive experience with families of drugs, at complex ages (late adolescents) and tired of taking ART [60].

It should also be noted that after transition, some patients have poor adherence to the health care system with failure to take ART, which in some circumstances leads to disease progression and in some cases (2% of the transition cohort) death [58].

In terms of associated comorbidities, we now know the importance of early treatment, which has been shown to prevent multi-organ damage from the first months of infection, as well as irreparable damage to the nervous system in children. HIV-infected children who are now young adults received cART after the first few years of life and thus neurocognitive impairment has been observed, but with good performance in daily life. Some neuroimaging studies have shown alterations in patients with good neurological function [61].

Cardiovascular comorbidity studied in a study of 150 perinatally transmitted HIV-positive 15-year-old adolescents found an increase in carotid intima media compared to matched healthy controls, an indirect marker of cardiovascular risk [62].

Bone comorbidity studied in a series of 98 adolescents aged 16 years showed 15% with decreased bone mineral density (BMD), although when adjusted for height, the percentage dropped to 4%. The prevalence of BMD decline correlated with CD4 nadir and CD4/CD8 ratio [63].

HCV co-infection, present in 12% of patients, has been treated with direct-acting drugs, with a cure rate of close to 100%, although 30% of patients have liver involvement (F3 and F4 fibrosis) [64].

In terms of sexual and reproductive health, women in the transition cohort have had a significant number of pregnancies, more than 60. In a study of 28 pregnant women, nine of them (32%) were at high risk of perinatal transmission because of a detectable viral load close to delivery. In this series, there was no transmission of HIV infection in the second generation thanks to the implementation of retention in care strategies and optimisation of ART [65].

Finally, a poorer quality of life as measured by validated SF12 questionnaires is observed compared to non-HIV young people. Thus in 39 young HIV+ verticals (mean age: 23.36 years, SD = 3.83) and 39 HIV- (mean age: 22.97 years, SD = 3.80), HIV+ patients were found to have lower scores on the physical health subscale than non-HIV (P = 0.001) and the general Spanish youth population (P = 0.006). HIV+ patients had lower scores on the mental health subscale (MCS) than the general Spanish youth population (P<0.001). Quality of life was better in HIV+ patients undergoing studies and worse for cocaine and cannabis use (P = 0.002) [66].

Conclusion:

Children born with HIV who are now adolescents and young adults are mostly in a controlled HIV status and need to be kept engaged with the health system and cART. The accumulated experience can help the new generations.

WHAT IS THE ECONOMIC COST OF HIV IN SPAIN AT THE MOMENT?

José Manuel Martínez Sesmero

The beneficial effect of antiretroviral therapy (ART) on HIV

infection and the impact on improving patients' quality of life is undoubted. However, its high cost in a resource-constrained environment makes it necessary to manage expenditure well.

A low CD4 cell count at diagnosis is associated with increased morbidity and mortality and higher costs. Patients with CD4 cell counts below 50 cells/microlitre generate a higher non-CART cost, which decreases substantially when CD4s increase above 100 cells/microlitre[31,48,51,66-72].

There are 146,000 people living with HIV in our country [21,72,73] who will require lifelong treatment. The total cost of ART has risen steadily since the inception of highly active ART, with the annual cost of ART being[30] 734,367,344 euros, and it has been estimated that ART accounts for 73% of the total lifetime health care costs of HIV patients in the US[74] and 87% in the first year in Spain [75].

The cost classification orders costs according to which agent bears them. Thus, costs would be grouped into costs for the health sector (basically those previously identified as health costs), costs for the patient and his/her family (most of the non-health costs: transport, time, etc.), and costs for other sectors (non-health costs borne by other public entities or by society as a whole, such as productivity costs), indirect costs [76].

Conclusion:

The cost of ART per patient per year varies significantly depending on the drugs chosen in the treatment regimen. The average annual cost per HIV patient has fallen considerably in recent years as a result of drug patent expiry and ART optimisation.

ECONOMIC BARRIERS TO HIV MANAGEMENT. GENERIC PHARMACEUTICALS

Inés Suarez García

Antiretroviral therapy (ART) has substantially increased the life expectancy of patients living with HIV [77,78], moving to considering HIV infection as a chronic disease in patients receiving ART with virological suppression. Adherence to ART is one of the key determinants of its effectiveness [79] and is of crucial importance given that treatment must be maintained throughout the patient's life.

In the wake of the last economic crisis, several regional health administrations and hospitals have imposed measures to reduce the cost of ART, such as setting an annual cost limit per patient or restricting access to some antiretrovirals. These measures have been applied differently in different autonomous communities in Spain and in some hospitals, producing inequities in access to different ART and being significantly associated with the use of ART regimens not recommended in clinical practice guidelines [69].

Generic drugs are drugs that have demonstrated bioequivalence to branded drugs, but cost less because the patent on the original branded drugs has expired[80]. These drugs have proven to be effective and have reduced morbidity and mortality where they have been used [81]. In recent years, some generic antiretroviral (ARV) drugs have begun to be marketed in Spain, with nevirapine, efavirenz (EFV), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), darunavir, ritonavir, and the combinations abacavir/3TC, emtricitabine (FTC)/TDF, and FTC/TDF/EFV currently available. In a context of limited resources for health care, the use of generics would enable a reduction in the cost of ART.

In the European Union, it is acceptable for a drug to be replaced by its generic equivalent if the generic equivalent has the same composition and pharmaceutical form as the original drug and has demonstrated bioequivalence with the original drug through bioavailability studies [80]. However, it is controversial to substitute a fixed-dose co-formulation (FDC) or a complete single-tablet regimen (STR) for its separate components (de-simplification or breaking of combos). The breakdown of complete single-tablet regimens is the main argument against the use of generic ARVs in clinical practice. Currently, the only full fixed-dose combination regimen of generic drugs available in our country is TDF/FTC/EFV; the other STRs used in ART are not currently available in generic formulation unless their components are administered separately [21,82-84].

De-simplification of STRs could lead to considerable financial savings, making it possible to allocate these resources to other health problems. A cost-benefit study using mathematical simulation estimated savings of $42,500 per patient and total savings of $920,000,000 for the US healthcare system if treatment with Atripla® (STRs including efavirenz, tenofovir and emtricitabine) were replaced by treatment with three separate daily tablets of generic efavirenz, generic lamivudine and tenofovir [85]. In France, another recent study has also shown that replacing ART regimens with generic drugs leads to considerable savings in health expenditure [86].

On the other hand, criticisms of these changes are based on the fact that switching to a higher number of tablets could decrease adherence and therefore the effectiveness of ART, and could favour the emergence of resistance [80]. Arguments in favour of using STRs include the simplification of treatment that would lead to a better quality of life for patients, and the reduced potential for resistance development by reducing the risk of confounding and the non-adherence to single drugs (selective non-adherence) [87]. The use of STRs has been associated with increased adherence[88-90] and a lower risk of hospitalisation [88, 89]. In this regard, a recent meta-analysis concluded that STRs were associated with better adherence, better virological response and lower cost than multi-drug therapy, but there was no difference in terms of immune response, mortality, adverse events or tolerability [90, 91].

However, most of the studies cited to support the greater effectiveness of STRs versus multiple daily tablets have been conducted in the context of simplification strategies, comparing STRs with other antiretroviral treatments that do not have the same composition or are even from different families (e.g. comparing an integrase inhibitor-based STR with a protease inhibitor-based or non-nucleoside-based pre-treatment).

There are very few studies that have compared the efficacy of STR treatment with the administration of its components (including generic equivalents) separately. Only 7 observational studies on STR de-simplification breakage strategies have been published. Six of them compared the administration of the brand-name drugs Atripla® [92-94], Atripla® and other fixed-dose combinations [95,96] and Triumeq® [97] with their separate components, and all found similar effectiveness. In addition, another study evaluated Triumeq® de-simplification in a single cohort of patients and found no virological failures at 48 weeks [98].

Although there is no conclusive evidence to show that de-simplification of STRs is associated with reduced treatment effectiveness, Spanish ART guidelines recommend the use of STRs [83, 99], and most physicians are not in favour of switching from STRs to their generic components separately: in a study in Spain, only 4.1% of physicians said they would never prescribe generic ARVs, but 53.3% would not do so if it meant increasing the number of daily pills. As for STR de-simplification, 63.9% of doctors think it would be associated with worse adherence and 42% with lower effectiveness [70]. However, in their latest update, European guidelines recommend the use of generic ARVs even if this means not using STRs [100].

Conclusion:

Generic ARVs have proven to be effective in the treatment of HIV infection and their use could lead to significant cost savings for the National Health System. Their use would imply switching from STRs to the administration of their components separately (de-simplification or breaking of combos), a strategy that is still controversial, which has led to a lack of widespread use of generic ARVs in our country. However, a small number of observational studies have shown similar effectiveness of the use of STRs with respect to their separate components. It would be desirable to create consensus criteria for the use of generic ARVs that include physicians, patients, and health administration.

WHAT IS THE REALITY OF "SLOW PROGRESSOR" PATIENTS?

Ezequiel Ruiz-Mateos

Long-term non-progressors are patients who are at one end of the spectrum of HIV infection progression. When we talk about progression, we mean no clinical progression and no immunovirological progression. Thus, they have high CD4+ lymphocyte counts comparable to the non-HIV-infected population and low or undetectable viral loads (VL) in the absence of antiretroviral therapy (cART). This has led to these subjects being considered as a model for the development of immunotherapeutic and vaccine strategies.

Traditionally, these individuals have been classified: A) from an immunological point of view: Long-term non-progressors (LTNP) with CD4+ cells >500 cells/mm^3 for more than 10 years in the absence of cART and usually with VL<5000 HIV-1 RNA copies/mL (~5%). B) from a virological point of view: subjects with low VL (<2000 HIV-1 RNA copies/mL, so-called viraemic controllers (VC)) or undetectable levels (<40 HIV-1 RNA copies/mL), elite controllers (EC) (<1%), for at least one year in the absence of cART.

Current cART aims for undetectability of VC, so in most cases VCs and LTNPs with detectable VC have ended up on cART. In relation to ECs, it was observed that it is a heterogeneous phenotype, with approximately 25% losing VC control and 40% having decreased CD4+ levels [101]. These findings, together with others in which ECs have been found to have a higher rate of hospitalisation, preferably for cardiovascular disease, than other non-controller subjects [102], have led to reconsideration of controllers as a model of persistent virological remission in the absence of cART or "functional cure". However, these findings are controversial, as in another cohort, the same authors did not observe such differences [103]. Nor have other large cohorts of controllers found a higher prevalence of cardiovascular disease and other non-AIDS events compared to non-controllers [104].

The key to this controversy is the heterogeneity of the controlling phenotype. ECs can be classified into transient controllers (TC), which are those that eventually lose control of the VC, and persistent controllers (PC), which are those that maintain control of the VC indefinitely [105,106]. Finding biomarkers that facilitate the discrimination of these two phenotypes is important for two reasons: 1) it allows us to design treatment strategies for TCs as they eventually progress, 2) it allows us to recognise PC as the true model of functional cure. In fact, different studies have shown that PCs have higher levels of HIV-specific T-response [105], associated with lower viral variability and diversity, along with lower levels of viral reservoir [105,107], and in turn, have lower levels of inflammation [105]. Additionally, it has been shown that these two phenotypes also differ in a peculiar proteomic profile associated with less inflammation in PCs compared to TCs, as well as a different metabolomic and lipidomic profile [71]. These results segregate PCs as the true model of persistent virological remission and, on the other hand, differentiate them from subjects who will lose spontaneous control and should therefore be identified as patients who should be offered treatment.

These findings shed light on the current controversy over whether HIV controllers should be treated with cART. Recent studies have shown that cART in controllers has been associated with a decrease in inflammation and immune activation in these subjects [108]. However, most of the subjects included in these studies were VC with detectable viral load. According to the results discussed above, in the case of a subject who has been infected for more than 30 years, with persistently undetectable CV and CD4+ cell counts above 500 cells/mm^3, the benefit of cART in this scenario would be more than doubtful, contrary to what would occur in the TC subject, where cART and/or complementary immunotherapeutic strategies would allow lowering the levels of inflammation.

Therefore, these data support PC as the correct model of functional cure to look to when trying to develop immunotherapeutic strategies. It is worth noting that in recent studies, 50% of the PCs failed to amplify the virus, and in those that did, the variability and diversity of the virus was very low [105]. Dating studies suggest that the evolution of the virus was stalled at a point very close to infection [105]. These findings suggest that perhaps some individuals managed to control the virus from the beginning and to some extent persistently stopped its replication, so that these subjects could be considered "functionally cured" or even some of them may have achieved a "sterilising cure", i.e. they managed to eradicate the virus. Regardless of whether this is the case, this small group of subjects with a persistent LTNP-EC profile constitute a true model of functional cure. Comprehensive analysis of virological, genetic and immunological factors in these subjects will provide important clues on how to achieve viral reservoir reduction and/or elimination and persistent virological remission in the absence of antiretroviral therapy in the general HIV-infected patient population.

Conclusion

Slow progressors or non-progressors are a peculiar group among HIV-infected people. Subjects with transient immunovirological control would be candidates for antiretroviral therapy and other complementary immunotherapeutic strategies, whilst those with persistent immunovirological control can be considered a model of functional cure or sustained virological remission.

WHAT IS AN HIV CURE AND HOW IS IT DOCUMENTED?

Javier Martínez Picado

Combination antiretroviral therapy is the current standard of care for HIV infection. When used daily, antiretroviral therapy effectively controls HIV replication, prevents the development of AIDS, increases life expectancy and reduces the risk of transmission. In 2019, approximately 26 million people had access to antiretroviral therapy, representing 68% of all infected people (UNAIDS 2020 report) [109].

However, current antiretroviral treatment is not curative, due to viral persistence in cellular and anatomical reservoirs that escape antiviral drugs or the immune system. Consequently, interruption of therapy results in rapid viral rebound in most infected people, necessitating lifelong treatment. Despite the undoubted benefits of antiretroviral treatment, it also has important limitations: (a) Drug toxicities, complex drug interactions (polypharmacy) and persistent immune dysfunction have significant health consequences; (b) Lifelong adherence to treatment is a challenge for many; (c) Resistance to antiretroviral drugs remains a problem, particularly for those who are not fully adherent to treatment; (d) Stigma is still associated with taking antiviral drugs; (e) Operational and logistical challenges related to involved drug distribution in many parts of the world are formidable, and the economic cost of providing antiretroviral treatment to all people living with HIV may be unsustainable in the long term. As the mortality rate among people living with HIV, due to the widespread use of treatment, declines faster than the number of new HIV infections, the prevalence of people living with HIV has grown significantly worldwide. In addition, the increasing number of people suffering at an older age (>60 years) is associated with a number of new challenges, both clinical and immunological. In the absence of an effective prophylactic HIV vaccine, as well as the challenge of treating more than 38 million people with sustained antiretroviral therapy, it is clear that new therapeutic strategies will be required for effective viral control, prevention or a potential cure. Therefore, there remains a critical medical need for research into new strategies to combat HIV, including the urgency of identifying an effective therapeutic intervention to control the virus in the absence of antiretroviral treatment and ultimately cure HIV [110].

In this context, multiple medical strategies are being explored to eradicate the replication-competent HIV reservoir ("cure") or to control viral rebound in the absence of antiretroviral treatment without HIV eradication ("sustained virological remission").

In recent years, we have learned that the viral reservoir is established soon after viral infection. However, early ART limits the size of viral reservoirs, reduces inflammation and immune activation, and reduces viral diversity in both adults and children, without necessarily delaying viral rebound if ART is stopped. Several compounds, called latency reversal agents, are being tested to assess their ability to reactivate latent viruses that comprise the main viral reservoir in subjects on antiretroviral treatment ("Shock & Kill" strategy). However, it is still difficult to find a balance between their specific efficacy in viral reactivation and their systemic toxicity. Immune therapies capable of facilitating cytotoxic T cell-mediated killing of infected cells, or antibody-mediated antiviral effect, sometimes in combination with latency reactivation agents, are also being explored. And finally, cell and gene therapies are also being investigated [111]. In this context, allogeneic haematopoietic stem cell transplantation for haematological malignancies contributed in 2007 to the first, and until recently only, case of complete eradication of HIV-1, the "Berlin patient", whose donor had a homozygous mutation in the CCR5 co-receptor for HIV that prevents HIV infection of the grafted cells[23]. In early 2019, a second case of HIV remission was announced in a person who has been off antiviral treatment since September 2017, as part of the IciStem project [112] (www.icistem.org), a multi-centre study to guide and investigate the potential for HIV cure in infected people requiring allogeneic stem cell transplantation due to severe haematological pathologies. However, due to its inherent risk, this strategy is neither scalable nor applicable outside the context of severe haematological malignancies and is therefore limited to a small group of HIV-infected individuals. The challenge is to adapt or find viral remission strategies in the absence of antiretroviral treatment that can reach as many people with HIV infection as possible.

Conclusion:

There is an urgent need to design and implement innovative strategies based on new molecular mechanisms to cure HIV infection by ending viral persistence. The aim is to improve the quality of life of HIV-infected people by reducing dependence on antiviral drugs, treatment burden and stigma.

WHY AREN'T VACCINES ARRIVING?

Beatriz Mothe

Despite multiple HIV prevention methods, including the use of antiretrovirals as PrEP, and the efficacy of current ART and its excellent tolerability profile, an estimated 1.7 million people acquired HIV in 2018 and still one third of the 38 million people living with HIV had not accessed ART according to UNAIDS. This is why the development of preventive and therapeutic vaccines for HIV remains one of the most urgent scientific challenges of our time [113].

One of the main difficulties for vaccine development lies in the great diversity of HIV globally. Subtype C infections accounted for 50% of infections in 2004. Subtypes A, B, D and G accounted for 12%, 10%, 3% and 6%, respectively; and recombinant subtypes 18%. The fact that different HIV subtypes can differ from each other by more than 30% in their viral genome makes the development of a universal vaccine very complex [114].

Still, in recent years, major advances have been made in the isolation and characterisation of monoclonal antibodies derived from B cells of people with chronic HIV infection against relatively conserved regions of the broadly neutralising HIV envelope glycoprotein antibodies (bNAbs). Some of these bNAbs target CD4 binding site epitopes, the V3 glycan, the V1V2 apex, the interface region of gp120 or the membrane proximal region of gp41, among others. The use of new single B cell culture methods, high-throughput neutralisation screenings and B cell sorting by flow cytometry with envelope antigens have been key to the isolation and generation of new bNAbs [115].

While progress is being made in understanding how bNAbs can be safely induced by a vaccine, several studies of passive infusion of bNAbs alone or in combination in the non-human primate model of infection using chimeric SIVs (SHIV) suggest promising results in terms of safety and protection, which is associated with the levels of neutralisation of the different antibodies [116]. Several Phase 2b clinical trials are already underway led from the HVTN/HPTN vaccine and prevention trials network (Antibody Mediated Protection (AMP) trials HVTN 704/HPTN 085 NCT02716675 and HVTN 703/HPTN 081 NCT02568215) and their results have just been published in 2021, demonstrating that passive infusion of antibodies can prevent the acquisition of infection of those strains sensitive to CRV01.

Of note is the first Phase 2b/3 clinical trial of a new preventive vaccine candidate that builds on the results of the Thai RV144 trial [117], which demonstrated modest (30%) - and short-lived - efficacy of protection in a Thai population at low risk of HIV acquisition. The new vaccines are based on the inclusion of mosaic immunogens, which, through bioinformatics optimisation, design HIV proteins with a number of sequence variants with the idea of inducing an immune response to a larger number of circulating viral variants. Studies in the NHP model have shown a vaccine efficacy of 60% associated with induction of large cytotoxic T-lymphocyte-mediated responses and high levels of monoclonal antibodies [118]. The results of the Phase 2b/3 studies are also being developed through the HVTN and results are expected over the next 3 years.

Finally, the complexity of designing new clinical trials of preventive vaccines following the progressive implementation of PrEP as a prevention measure in populations at high risk of acquiring HIV, both in terms of sample size, implementation and ethical issues, should be emphasised.

The development of a therapeutic vaccine aims to achieve control or complete eradication of HIV from the body without the need for ART. This objective must be achieved through a strategy that is equal to (or better than) the ART, both in terms of cost and accessibility, but above all in terms of security, which sets the bar for non-inferiority very high.

One of the main obstacles to the development of a therapeutic vaccine is also the viral diversity, in addition to the viral subtypes, some of the variability is due to immunological adaptation. HIV mutates and escapes relatively easily from the pressure exerted by cytotoxic T lymphocytes (CTLs) mediated by individual HLA molecules. Therapeutic vaccines must therefore be effective in different locations with different circulating viruses and in populations with widely differing genetic backgrounds [119]. To combat such immense diversity, new immunogen designs are based on attempting to re-educate the HIV-specific immune response against those regions of HIV that are highly conserved among the different viral subtypes responsible for generating highly functional HLA-independent cytotoxic responses [120,121] and are currently in clinical phases of development.

Another major obstacle in the field of HIV cure lies in the relative degree of immunodeficiency of people with HIV infection. High levels of chronic inflammation lead to persistent immune depletion that significantly limits the functionality of CTLs and the longevity of vaccine-induced responses. This is why we often see early clinical trials of new vaccine candidates in groups of patients treated in the earliest stages of HIV infection, whose levels of viral escape and immune depletion are lower than after years of chronic infection. With new developments in the field of immunotherapies in oncology and autoimmune diseases, the combination of therapeutic vaccines with immunomodulatory agents of the immune response is expected to be explored.

Finally, the viral reservoir - made up of latently HIV-infected cells that are relatively invisible to the immune system - is a major source of viral rebound once ART is stopped.

Most likely, neither eradication nor a functional cure of HIV can be achieved without eliminating or achieving very low levels of viral reservoir while inducing a highly functional and long-lasting immune response [122].

Conclusion:

The enormous viral diversity and the somatic hypermutation required to induce antibodies with broad neutralising capacity make the development of effective preventive vaccines against the different HIV viral strains extremely difficult. Alternatively, promising results in primate models suggest that passive administration of monoclonal antibodies may have high protective efficacy.

HOW FAR SHOULD WE GO WITH RISK BEHAVIOUR PROPHYLAXIS?

Pep Coll

We now have proven prevention tools that we must use if we are serious about ending the HIV epidemic. A very important and relatively new tool that is changing the prevention paradigm is PrEP.

Until just over 7 years ago, the main preventive tool available was the condom, which has prevented countless HIV infections, but has not stopped the flow of new infections.

We now know that the combination of two antiretrovirals (tenofovir, disoproxil, fumarate and emtricitabine) can prevent infection in people exposed to HIV, with close to 100% effectiveness, provided there is correct adherence to the medication. This is the so-called oral PrEP, which has been approved in the National Health System and which was the great unresolved issue in our system. Such is the evidence available on the efficacy of PrEP that its recommendation [123] is included in most clinical guidelines: the first was published by the US Centers for Disease Control and Prevention in 2014. In 2015, the World Health Organisation stated that PrEP should be offered to all populations at higher risk of HIV infection. It points out that PrEP should be a prevention option in addition to condom use, promotion of HIV testing and counselling, treatment as prevention, male circumcision and harm reduction strategies for people who inject drugs.

Other guidelines, such as those of the European AIDS Clinical Society' and GeSIDA [124], also recommend PrEP for those who may be at higher risk of infection [125].

The Spanish Bioethics Committee has come out in favour of the introduction of PrEP[126], stating that it is ethical to fund it. The Committee sees this as a case similar to others, such as tobacco, noting that "at no point in the tobacco control debate was there the option of limiting or excluding access to health care for those who had irresponsibly put their health at risk by smoking". This means that we cannot deny a person access to a powerful preventive tool because he or she engages in risky behaviours, or rather what we label as such, with all the stigmatising burden that this can entail.

It is important to note that people who seek PrEP do so because they want to protect themselves, and that in general they want a healthier sex life, without the ongoing threat of HIV. Recall that, according to the World Health Organisation, sexual health is not only the absence of disease but also a state of physical, emotional, mental and social well-being in relation to sexuality. And PrEP shows that users can have a more pleasurable sex life.

But there are still voices arguing that PrEP should be used with caution because it will "open the door to promiscuity" and condom use will be abandoned, with all its consequences. It is true that there is concern about a possible increase in the incidence of other STIs due to so-called "risk compensation", i.e. the adoption of higher risk behaviours (non-use of condoms, increased number of sexual partners, etc.). In this regard, it should be noted that while most clinical trials of PrEP have not observed such "risk compensation", there are implementation studies in which an increase in STIs is observed. In any case, we must bear in mind that this increase has been registered in Spain and other countries for years before the implementation of PrEP, so this increase in STIs cannot be attributed to PrEP, or at least not in its entirety. There are other factors that may influence this increase.

What needs to be done is to implement strategies to counteract this potential increase. One such strategy is regular screening for STIs, which allows early detection and treatment of STIs, many of which are asymptomatic, thus helping to break the chain of transmission. In this regard, some studies show through modelling that regular screening can reduce the incidence of STIs. We also know that the presence of STIs increases the risk of HIV infection, which further supports the recommendation for such screening.

It should be emphasised that PrEP is not only about administering the drug, but also includes follow-up of users, which is an excellent opportunity to maintain contact with health services, allowing for STI screening, counselling and sexual health education, detection of other health problems, e.g. drug use.

PrEP is therefore not synonymous with abandoning condom use, which must continue to play an important role, but is a powerful preventive tool as part of a broader, holistic prevention strategy. At this early stage of the implementation of PrEP in our National Health System, it is essential to promote and facilitate access to PrEP for all those at risk of HIV infection. This requires providing adequate information to the population, especially potential beneficiaries, but also awareness raising and training of health professionals on PrEP.

The challenge is to implement and reinforce all proven effective preventive strategies. If we can, we can dramatically reduce HIV infections, as is already being seen where such strategies are being implemented.

Conclusion:

Pre-exposure prophylaxis (PrEP) with antiretroviral drugs is proving highly effective in HIV prevention. Possible "side effects", such as an increase in Sexually Trans-

mitted Infections, are not a reason not to recommend it, but to look for strategies to counteract this potential effect.

COULD YOU SUMMARIZE THE CONTRIBUTIONS OF THE MAJOR GROUPS OF ANTIVIRAL AGENTS?

Esteban Martínez

There are four major groups of antiviral agents that have been used in the treatment of HIV infection: nucleoside analogues (NAs), protease inhibitors (PIs), non-nucleoside analogues (NANs) and integrase inhibitors. All of them have played a very important role throughout history [83].

ANs were the beginning of treatment for HIV infection. They were first used as monotherapy, then in dual therapy and even triple therapy. However, suppression of viral replication was suboptimal and clinical benefit was limited. Toxicity had a common mechanism of mitochondrial dysfunction with varied clinical manifestations. The vast majority of antiretroviral regimens have included AN. ANs are components of standard antiretroviral treatment.

PIs changed the natural history of HIV infection. Its pharmacokinetics were improved by boosting with low-dose ritonavir and later with cobicistat. Potentiation allowed PIs to have a high genetic barrier so that resistance mutations were not generated, but also gave them a higher risk of interactions. The toxicity of PIs has generally been digestive and metabolic. Because of their potency and genetic barrier, PIs were the forerunners of the less-than-three-drug regimen.

NANs have had better tolerability and less risk of interactions than PIs. In addition, they have a long half-life, which makes them easy to dose. Unlike other groups, the drugs in the NAN group have generally been able to be taken once a day. In addition, their prolonged half-life has meant that suppression of viral replication can be better maintained than with PIs in cases of occasional suboptimal adherence. Therefore, PIs have been used preferentially in first lines of treatment for many years. However, their low genetic barrier is responsible for the emergence of resistance mutations when viral replication is not suppressed. Familial toxicity is hypersensitivity and, in the case of efavirenz, neuropsychological disturbances that may appear late [100].

Integrase inhibitors combine favourable characteristics of both PIs (genetic barrier, potency) and NANs (simplicity, tolerability), but also have a faster virological suppressive effect, better long-term tolerability, and little risk of interactions. These are currently the preferred antiretroviral treatment components. Toxicity includes neuropsychological disturbances, usually mild and transient, and weight gain.

Conclusion:

Nucleoside analogues are common components of antiretroviral therapy. Protease inhibitors have a high potency and high genetic barrier. Non-nucleoside analogue drugs have a long half-life and simple dosing. Finally, integrase inhibitors have favourable characteristics of both PIs and NANs, but also have a faster virological suppressive effect, better long-term tolerability, and little risk of interactions.

PARENTERAL ANTIRETROVIRAL THERAPY: HOW OFTEN? COULD IT BE ANNUAL?

Miguel Górgolas

Parenteral antiretroviral therapy is now, fortunately, a reality. Long-acting parenteral treatment is available with great success for some chronic diseases, such as schizophrenia, or as a method of contraception. There are many reasons that support its suitability for the treatment of chronic infection in people living with HIV. On the basis that the patient should not be injection-phobic, parenteral treatment has, "a priori", a large number of advantages over oral treatment. Firstly, it can be expected to facilitate good adherence or compliance, as it is, in a way, a form of directly observed treatment administered by health personnel. Secondly, the fact of not having to take daily medication allows the patient to "forget" about the infection and live a completely normal life. Thirdly, it is more than likely to lead to a reduction of the stigma that, unfortunately, still exists for many patients who can sometimes be challenged by the simple fact of having to take daily medication.

Currently, the most advanced development consists of a parenteral treatment based on the administration of two drugs, cabotegravir and rilpivirine, which share the appropriate pharmacokinetic characteristics to be co-administered to achieve high antiviral potency, slow release and low metabolic clearance, allowing for administration every 2 months. This type of treatment is called CARLA, an acronym for Cabotegravir + Rilpivirine + Long + Acting.

The first study of this combination, the LATTE-2 trial explored the safety and efficacy of the combination as a maintenance treatment, as well as finding the optimal dosage for subsequent phase III trials. Patients without prior antiretroviral treatment received a 20-week induction treatment with oral CAB+ABC/3T. Those who achieved an HIV-1 viral load <50 cop/mL were randomised to one arm of parenteral treatment every 4 weeks, another arm every 8 weeks and another arm continued with oral treatment. The conclusion was that CARLA demonstrated its ability to maintain undetectable viral load when administered every 4 or 8 weeks [22]. Subsequently, a phase III trial (Flair trial) was conducted in ART-naïve patients who received an effective induction course of DTG/ABA/3TC for 20 weeks followed by cabotegravir and oral rilpivirine for 4 weeks, before switching to parenteral treatment. Those patients who agreed to participate in the study were randomised to receive either CARLA every 4 weeks or continue with oral DTG/ABA/3TC. The efficacy of CARLA was similar to conventional oral treatment and local tolerance of the injections was good, being better tolerated in successive administrations throughout the study [127]. Notably, 97% of patients

who agreed to participate in the study and received CARLA preferred the intramuscular regimen to the oral regimen they had taken during induction. Only three patients in the CARLA arm had confirmed virological failure with development of resistance mutations against NNRTI and INSTI. All three patients had the same subtype (A1), a baseline mutation in INSTI (L74I) and concentrations of both drugs below the averages of the treated population. The impact of these findings is being investigated, but does not seem likely to change the good results obtained.

Two similar studies, but with previously treated patients with undetectable viral load (Atlas Trial -every 4 weeks- and Atlas 2M Trial -every 8 weeks-), i.e. "switch" studies, have also demonstrated non-inferiority of CARLA to different oral treatment regimens based on PIs, NNRTIs or integrase inhibitors. Similarly, the satisfaction of patients treated with CARLA is very high. The frequency of discomfort at the drug injection site was high in the first few injections, but as in previous trials, tolerance improved over the course of the study. Again, the number of confirmed virological failures in the CARLA group was very low (1%), so that only three patients had RPV-resistant mutations, some of which were achieved from the start of treatment [128,129].

The Atlas and Flair studies on CARLA have been able to demonstrate that patient adherence has been very high, with up to 98% of injections being administered within the scheduled 7-day window. In addition, none of the patients who received treatment beyond 7 days had virological failure. Finally, the possibility of a transitional oral treatment was also explored, in case the patient could not receive the intramuscular dosage, and the result has been satisfactory [130]. In addition, the stigma experienced by people living with HIV may be alleviated by the possibility of switching from oral to injectable treatment, particularly when administered as a long-acting treatment such as CARLA [131].

But progress does not stop there, that is only the beginning. Ideally, a treatment should be available that can be administered, or better, self-administered parenterally, e.g. subcutaneously, or via a slow-release reservoir, every three, six or even twelve months. There are three molecules at different stages of development that could be used in this way. A potent capsid inhibitor (GS-6207) with a half-life of more than 24 weeks and activity against virus resistant to other antiretroviral families, which could be administered subcutaneously. This new drug in development has many advantages. Firstly, it has a novel mechanism of action acting on several targets in capsid function; secondly, it could be used in patients previously treated with several families of antiretrovirals and with virus resistant to them; and finally, due to its long half-life it would allow administration possibly every 6 months. Results to date suggest that a single dose (50-450mg) of GS-6207 administered subcutaneously has potent antiviral activity, with a 1.8-2.2 log10 copy/mL reduction in viral load over 10 days. In addition, the drug was safe, with few mild side effects at the injection site, making it a good candidate for further clinical development [132, 133].

A new highly potent antiretroviral reverse transcriptase translocation inhibitor (MK-8591) with a half-life of more than 180 days, which could be administered once a year via an implant, is under study. This molecule maintains its activity against viruses with resistance to other reverse transcriptase inhibitors, with mutations such as K65R, M184V or M184I. A single 10 mg dose achieves an average reduction in HIV-1 viral load of 1.6 log in 7 to 10 days [134].

The main challenge for these drugs is to properly assess with which other drugs they should be combined in order to obtain a truly effective ART that can be administered once or twice a year. In this sense, the pharmaceutical industries have a double challenge: on the one hand, to develop the molecule and, on the other hand, to reach agreements with other companies to build an effective combination.

Finally, administration of neutralising antibodies administered subcutaneously or intravenously on a regular basis could be another parenteral treatment option, preliminary studies of which have already begun [135].

Conclusion:

Parenteral treatment of HIV infection is a reality that will soon materialise. Its efficacy is similar to conventional oral treatment and allows patients to receive the medication every 8 weeks. The combination of cabotegravir and rilpivirine is the most developed so far, but other promising molecules are in development.

REDUCED DRUG SCHEDULES?

Federico Pulido

Since 1996, antiretroviral treatment has consisted of a combination of three drugs. The reason for this number was due to the need to achieve sufficient efficacy to suppress viral replication, without giving the option to select for possible viral variants carrying resistance mutations that would lead to treatment failure, thus maintaining suppression indefinitely. As a result, immune impairment was reversed, leading to a dramatic decline in the morbidity and mortality associated with HIV infection. With the drugs available at the time, this could only be achieved by combining three drugs, although it is true that not all three-drug combinations are equally effective.

The emergence in later years of more potent antiretroviral drugs with a higher barrier to resistance led to the possibility of using combinations with fewer drugs. This strategy of reducing the number of drugs as long as it does not lead to a loss of efficacy was motivated by the possibility of reducing toxicities (those derived from the drug that is no longer used) and reducing the cost of treatment [136].

Attempts to use a single potent drug with a high barrier to resistance (boosted protease inhibitor) failed to match the antiviral efficacy achieved with the same drugs in triple combinations for maintenance of virological suppression. However, suppression was maintained in a high number of patients and

the small number of patients whose viral load rebounded did not select for resistance [137].

Two-drug strategies have produced heterogeneous results, depending mainly on the drugs used in the combination and the patient's therapeutic history[138]. We now have evidence from large randomised clinical trials that some two-drug combinations have the same efficacy in controlling viraemia in previously untreated (naïve) patients and/or maintaining virological control in viraemia-suppressed patients as the best available triple-drug regimens [67,139].

These successful two-drug combinations have in common the presence of a drug with a high barrier to resistance (a boosted protease inhibitor) and/or a second-generation integrase inhibitor, with the addition of a reverse transcriptase inhibitor (nucleoside analogue or non-nucleoside analogue) as a second drug [140].

Today, therefore, highly (and equally) effective antiretroviral regimens composed of two or three drugs are available, with the efficacy of the regimen depending not on the number of drugs used, but on which drugs are used in the combination. The discussion on the required number of drugs [137,138] should therefore be ended, in order to focus on the efficacy and tolerability demonstrated by each specific regimen.

Conclusion:

It is no longer the number, but the type of drugs that determines the effectiveness of antiretroviral treatment. We currently have guidelines with two drugs whose efficacy and tolerance allow them to be used in clinical practice.

WHAT IS THE FUTURE OF IMMUNOTHERAPY?

Maye Coiras

The progression of HIV infection is highly dependent on the timing of cART initiation as it conditions the preservation of a functional immune response. In fact, the lymphocytopenia and immune dysregulation associated with HIV infection are responsible for the development of opportunistic infections and various types of HIV-associated tumours. In particular, during antineoplastic treatment of HIV+ patients with different immunotherapies, it has been observed that some may be useful against viral persistence by affecting HIV latency mechanisms and activating a specific antiviral immune response [141].

To address the different immunotherapy strategies that might be useful for the control of HIV infection, we need to consider the central target of infection: CD4+ T cells. Blocking the binding of the virus to the cell by neutralising antibodies is a potential immunological tool to prevent infection. Approximately 20% of patients untreated for at least 2 years develop broad spectrum neutralising antibodies (bNAbs) that allow cross-neutralisation of different virus types [142]. This is due to the continuous maturation of affinity against conserved and accessible Env epitopes that evolve as a result of immune pressure. 1% of patients who develop bNAbs are elite controllers. Among the main functions of bNAbs are virus neutralisation and Fc-dependent antiviral activity, such as antibody-dependent cellular cytotoxicity (ADCC) [143]. Meanwhile, bNAbs such as VRC01, 3BNC117 and 10-1074 have been shown to be safe and well tolerated after intravenous infusion [144-146]. They induce a significant reduction in viraemia and require less continuous administration than cART. However, the protection they induce is not long-lasting and regular infusions are necessary. In addition, combinations of several bNAbs should be administered to improve efficacy and avoid the emergence of resistant variants, and it is necessary to assess in advance whether the patient's viral variants are sensitive to the combination of bNAbs [147,148]. On the other hand, bNAbs can be used for the reverse generation of vaccines and the development of alternative gene therapy strategies to vaccination is being considered [148,149].

On the other hand, the mechanisms of infection developed by HIV lead to a state of immunosuppression that hinders an effective immune response. In this sense, the expression of molecules related to immune control such as CTLA-4 or PD-1/PD-L1 have been described as possibly responsible for this immune dysfunction during infection. In fact, the expression of these molecules increases during chronic infection and PD-1+ cells contain more viral DNA and RNA [150,151]. Therefore, immune checkpoint inhibitors (ICPIs) could be useful for boosting an antiviral and antitumour response and have already been used to treat some HIV-related malignancies [152]. Anti-PD-L1 drugs appear to transiently increase CD4 viral transcription, followed by a reduction in plasma viral RNA [141]. Combining pembrolizumab with latency-reversing agents (LRAs) such as bryostatin would increase HIV replication from reservoir cells without activation and proliferation [151].

To improve the visibility of reservoir cells, specific markers need to be identified. CD30 is a marker of latently infected but transcriptionally active cells and could therefore be a therapeutic target for HIV-1 eradication [152]. In fact, treatment with the anti-CD30 antineoplastic drug brentuximab vedotin has been associated with a reduction in plasma viraemia [153]. On the other hand, homeostatic proliferation of the reservoir by cytokines such as IL-7 is one of the main obstacles to HIV-1 eradication. IL-7 levels increase during HIV-associated lymphocytopenia and decrease with immune reconstitution, so administration of IL-7 to aviremic patients increases viral load and CD8 activity [141]. IL-15, another proliferative cytokine produced during acute infection, can also induce NK cell stimulation and proliferation of CD8+ T cells for the destruction of latently infected CD_4 T cells [154].

Finally, tyrosine kinase inhibitors (TKIs) used for the treatment of chronic myeloid leukaemia have been shown to have a potent antiviral effect against HIV by acting on different cell types: they prevent ex vivo CD4 infection by preserving the antiviral innate immune factor SAMHD1; interfere with IL-2- and IL-7-induced CD4 homeostatic proliferation, which may prevent reservoir turnover; and induce enhanced cytotoxic activity by increasing CD56+ and TCR+ cell populations [68,155,156].

Conclusions

Immunotherapy should be considered a very important tool for the control of HIV infection. New advances in neutralising antibody therapy and its application to vaccine development are encouraging, although some issues related to stability and efficacy still need to be addressed. On the other hand, immune-enhancing drugs such as immune checkpoint inhibitors could make reservoir cells visible to the immune system and enhance the antiviral effect of cytotoxic cells, as could tyrosine kinase inhibitors. Improving the immune response is therefore essential for a functional cure of HIV by exerting better control of the reservoir.

WHAT IS THE FUTURE OF HIV SPECIALISTS?

José Ignacio Bernardino

With the full implementation of pre-exposure prophylaxis, early diagnosis, prompt treatment initiation and combination prevention strategies, new HIV infections will gradually decline. As has already been demonstrated in other cities such as London, Paris and San Francisco, HIV specialists in HIV units must take the lead in these initiatives together with other health stakeholders and public health officials. An inescapable and achievable goal is to reach zero new HIV infections in Spain.

With the decline in new HIV infections, the need for specialised HIV units may be questioned. The stigma associated with the infection, unfortunately still very present in our society, together with the general lack of knowledge about HIV infection, even among health professionals, will require the continuity of specialised units. We cannot forget that a significant proportion of new infections come from vulnerable populations such as transgender women, injection drug users and illegal immigrants, adolescents at risk of social exclusion who are often excluded from the health system and who receive social and health care in community centres, sexually transmitted disease clinics, drug user centres and specialised HIV units. The maintenance of these centres is essential for the social and health care of these groups.

At present, the life expectancy of HIV-infected people is similar to that of the general population, so the number of people with HIV infection being followed up in the units will be increasing and this translates into a change in care needs. Growing older with HIV infection, the comorbidities associated with this process, and in short, the chronicity of the different pathologies that can converge in a person with HIV infection, requires a multidisciplinary approach that must be coordinated by the HIV infection specialist. This new landscape is a unique opportunity to lead the transformation of the healthcare system from an outdated and hugely expensive acute care model to a more modern day chronic care model. In these models it is essential to place the patient at the centre of care. A model in which the agents involved coordinate and focus their care on the patient, sharing the same information systems with multidirectional and reciprocal communication channels between patient, professionals and administration is a pending issue in many parts of our country. The elimination of the existing fragmentation between levels of care and different health professionals and the growing use of new technologies and the e-health revolution will help to make the system more efficient and encourage self-care with greater co-responsibility and more active patient participation in the management of their health [157,158].

The enormous efforts of scientists in HIV vaccine development and eradication of HIV infection make close collaboration between HIV clinicians and basic science researchers essential.

Specialists in HIV infection together with other health professionals and community agents continue to work tirelessly to achieve zero new HIV infections in Spain, to eliminate the stigma associated with HIV infection and to achieve the not impossible, but still distant, eradication of HIV infection.

Conclusion:

Specialised HIV units will continue to be indispensable in the coming years. However, there will be a shift from the current, exhausted, acute patient-centred model to a more efficient model focused on chronic patient care. Experts should continue to contribute to maintaining the high standards in HIV research.

WHAT REMAINS TO BE DONE IN HIGH-INCOME COUNTRIES?

Santiago Moreno

The treatment currently prescribed for people with HIV infection is close to optimal, both in absolute terms and relative to the treatment of other chronic diseases. HIV infection is among the diseases for which treatment is available with the highest rate of therapeutic efficacy and the least toxic effects and the greatest impact on the health status of the recipient. Antiretroviral treatment has not only enabled people with HIV infection to have a life expectancy similar to that of the non-HIV-infected population, but to do so with a good quality of life without limitations that might result from the disease itself or from the medication.

In the current situation, it is difficult to improve the treatment of the disease. The prospect of long-acting drugs that will soon allow dosing at extended intervals of several weeks or months will certainly be an improvement, but not a dramatic change. Improving antiretroviral treatment is not really the most important issue at hand, nor is it the most pressing. The most immediate ambition is to achieve a cure for those infected and, even more ambitiously, the availability of a vaccine whose administration to those at risk would prevent them from becoming infected. These are clearly two outstanding issues in the fight against HIV in industrialised countries and globally. Their achievement is not on the near horizon and we are therefore faced with more immediate problems still to be solved.

The reality we live in our society, and that of people living with HIV infection in particular, requires solutions to identified, well-known, unresolved issues. These are issues that have to do with controlling the epidemic in our environment and improving the quality of life of people living with the infection. In industrialised countries, there remains a high risk of HIV transmission among people who engage in risky practices, primarily unprotected sex, but also among injecting drug users who share injecting equipment. Whatever the route, transmission occurs primarily from people who do not know they are infected and are therefore not receiving antiretroviral treatment. Identifying infected persons and administering antiretroviral treatment to achieve control of viral replication could stop transmission, reduce the incidence of new infections and, overall, control the epidemic with all the associated benefits [159]. It is difficult to understand why, having demonstrated the benefits of diagnosing and treating infected persons, the necessary procedures have not been put in place to achieve this goal. At present, most countries, including Spain, rely for diagnosis on the identification of antecedents or risk practices, which has clearly proved to be insufficient.

In order to bring the epidemic under control, it should be noted that the proposed measure of identifying all infected persons as early as possible and treating them, although the most important, is not sufficient. In the meantime, other measures are needed to limit the transmission of the virus. An effective method of prevention has also been described for this. PrEP has shown efficacy in preventing infection in uninfected people who engage in risky practices not only in clinical trials, but also in real life. Recent population-based experience has shown that PrEP administration is associated with a significant decrease in the incidence of HIV infection, regardless of the percentage of patients with an undetectable viral load [160]. In Spain, this measure has been approved.

Improving the quality of life of people with HIV infection, which is another unfinished business, has nothing to do with the quality of life associated with health status. People on antiretroviral treatment are healthy enough to lead normal social, family and working lives. The quality of life they lack is related to the stigma attached to being HIV-positive and the discrimination they face at many levels, creating real social inequalities [161]. Again, it is inexplicable that in "first world" countries, suffering from a chronic illness can become a reason for discrimination. In this case, the way to combat it is more complex, but it is undoubtedly where a society such as ours is most likely to demonstrate the ability to solve problems that are not easy and that affect a large number of people.

Conclusion:

In neighbouring countries, HIV infection still presents challenges that have not yet been overcome. Beyond the limited room for improvement in antiretroviral therapy or the achievement of desired HIV cures and vaccines, society and people living with HIV infection need action to achieve urgent goals. Control of the epidemic in an environment such as ours can be achieved if measures of known efficacy, such as early diagnosis and treatment of infected persons, are implemented and PrEP is administered to all persons with an indication. In addition, combating the stigma and discrimination still faced by people who are HIV-positive is the second major issue that all first world countries have yet to address.

WHAT REFLECTIONS FROM AN ETHICAL POINT OF VIEW ARE RAISED?

Diego Gracia

It is not possible to talk about the ethics of HIV without recalling the heroic years when a clinical AIDS diagnosis meant a death sentence, usually within fourteen months. This was the case for most of the 1980s. In addition to being an acute and deadly disease, its rapid spread led to it being labelled as "epidemic", triggering uncontrolled fear among health professionals and the general population, in some cases to the point of panic. In such a critical situation, conflicts have soared, and so has ethical reflection. It was common to see articles on ethics in large clinical journals, such as the New England Journal of Medicine, Annals of Internal Medicine, JAMA, Lancet or the British Medical Journal, in a previously unknown proportion. In those days it was not uncommon to say that only with the example of AIDS was it possible to explain the main chapters of an entire ethics course. There were many very serious problems related to a key element of clinical activity: diagnosis. Thus, whether or not it was obligatory to ask the patient's permission to carry out the diagnostic test, given that the professional considered himself to be at risk and therefore believed he was entitled to know if the patient was HIV-positive, even against the patient's wishes. Another serious problem was that of data confidentiality, especially in view of the need to protect patients' sexual partners. No less serious were the problems related to treatment: Were health professionals obliged to assist them, or could they raise any objection? The WHO itself had to intervene by reminding professionals that they were obliged to assist, and that the risk was minimal as long as they took the recommended protective measures into account. Another serious problem was the dispersion and distribution of treatments when they became accessible, given their high cost. No less serious were the conflicts that arose with the testing of new antiretroviral drugs in Asian and African countries. And the list could go on.

Today things are very different. HIV infection has gone from being an acute to a chronic disease, from epidemic to endemic, and from being seen as a public health issue to a private hygiene problem. The latter is something that is rarely reflected upon, yet is becoming increasingly important. I will therefore focus my analysis on this point.

Western medicine did not have truly effective therapeutic resources, both medical and surgical, until the 19th century. It was then that experimental pharmacology and pharmacological therapeutics appeared as disciplines, and when surgery began to succeed in its incursion into the three cavities of

the human body, the abdominal, thoracic and cranial cavities, thanks to the three great novelties introduced in the second half of the century: antisepsis and asepsis, anaesthesia and haemostasis. For the first time in history, the doctor saw himself as being able to cure diseases. Add to this that from the end of the 18th century, as a consequence of enlightened despotism, governments began to turn health into a political objective, which led to the birth of what was first called Sanitary Police and later Sanitary Policy or Public Health.

This revolution was so far-reaching that the strategies developed by physicians from antiquity until the end of the 18th century were no longer of interest. Given their very limited therapeutic arsenal, classical physicians sought above all to promote the health of the population by means of very simple and elementary procedures for promoting private hygiene, i.e. health education. Based on a Hippocratic treatise entitled On Airs, Waters and Places, the physicians gradually drew up a catalogue of six major chapters for the promotion of private hygiene. This is what was known in the Middle Ages as the catalogue of unnatural sex res non naturals. The six chapters were: environment (what the Hippocratic writing On Airs, Waters and Places referred to), food and drink (cibus et potus), movement and rest (motus et quies), sleep and wakefulness (somnus et vigilia), excretions and secretions (excreta et secreta) and psychic disorders (affectus animi). Prudent management of these six major chapters was the best way to promote health and prevent disease. Especially chronic disease, because chronic disease has a lot to do with unwise lifestyle management. If a person frequently overeats, he or she will almost certainly become overweight, which in turn predisposes him or her to certain chronic diseases, such as type II diabetes.

As hardly anyone remembers this history anymore, it is worth pointing out that this catalogue was fully valid until the end of the 18th century, and that in the last two hundred years that it has been losing importance in the estimation of doctors, given the progress of diagnostic and therapeutic techniques and the no lesser increase in public hygiene, until it has practically disappeared. However, it is still valid in the case of chronic illnesses, as these are most often caused precisely by a disorder of habits, i.e. lifestyle habits.

HIV infection is now a chronic disease, one of the so-called "sexually transmitted diseases" (STDs). These diseases also have a long history, from which we can perhaps learn something. For example, we can learn from the fact that they were called "moral, secret or shameful diseases". Moral diseases were not so much because they were against good morals, but because they were caused by the disorder of what Latin-speakers called mores, customs. They were diseases directly related to lifestyle habits. This is why they were placed, within the catalogue of unnatural sex res non naturals mentioned above, in the chapter entitled excreta et secreta. These were not exclusively medical problems, but primarily social and cultural issues. The paradigmatic example of STDs during the modern centuries was syphilis. It began to be controlled at the beginning of the 20th century with the appearance of the first synthetic chemotherapy drug, salvarsan, and was given the coup de grace in the middle of the same century with the appearance of penicillin. This was so revolutionary that the 1960s witnessed a profound change in social and cultural habits known as the "sexual revolution". The old controls were relaxed, and "repression" was replaced by permissiveness or "sexual freedom". From one extreme to the other... Until 1981, when HIV infection appeared on the horizon. It started out as a very acute and aggressive disease, which medicine had to control, of course, through new therapies. And this it did. The pace of new drugs and their increasing efficacy has dramatically changed the landscape of the disease over the course of a few decades. But medicine is not finished with it. What has been achieved thus far was its transformation from an acute to a chronic disease. It would therefore seem that the time had come to turn to the strategies that are most appropriate and effective in this type of disease: those that have to do with lifestyle and risk practices. It was time to remember the old story of sex res unnatural. By then, however, the old historical references had been lost, and there was a growing conviction that HIV infection was a purely medical, or rather a pharmacological, problem. Instead of acting on risky practices, it was sufficient to protect oneself by using chemical, physical or pharmacological agents.

It is doubtful that this is the only, let alone the most appropriate strategy to control this infection. Some data are alarming to say the least. One of them is the change in leisure practices, shifting from daytime to night-time, in which in order to resist the fatigue of a sleepless night it is necessary to drink alcohol ("binge drinking") and take stimulant drugs, which in turn diminish self-control, disinhibit sexuality and lead to irresponsible practices which, moreover, tend to be practised in groups, thus producing the "herd" effect, in which individual responsibility is diluted within the group dynamic. All this leads to an irresponsible management of the body, consumption, and sexuality. In the latter, from "sexual repression" one moves to "sexual disinhibition", which uses the other person as an object, or as Kant would say, as a pure "means" and not as an "end" in itself. Humans are moral and not merely natural beings, precisely because we have the status of an "end" and not merely a "means" to be used at the whim of others. Sexuality, like food and alcohol, must be managed wisely. Prudence is the capacity for self-control, and it is responsibility in the management of one's actions and life. And it is also health, private health, something that needs to be promoted through education; through education in general, and also through health education. Health professionals are also educators, and in matters such as those we are analysing here, essential educators. The aim of medicine is not only to cure disease, but to promote health and the prudent and responsible management of the body. At a time when we are approaching the ideal of precision medicine or personalised medicine, we cannot forget that there will be no personalised medicine without educating people in the responsible and prudent management of their bodies and sexuality. This is something that the ancient physicians knew very well, and which today's therapeutic potential is unfortunately making us forget.

Conclusion:

The enormous effectiveness of therapeutics, both pharmacological and surgical, and the healthcare importance of public health programmes and health policy, is making us forget something that in traditional medicine was the most important objective of the practitioner's action: namely, education and promotion of private hygiene. This is worth remembering at a time when HIV infection is no longer an acute and potentially life-threatening disease, but a chronic disease, where it is essential that patients learn to manage their bodies wisely and responsibly, normalising their behaviour and avoiding risky practices.

FUNDING

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

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. Pneumocystis pneumonia--Los Angeles. 1981. MMWR Morbidity and mortality weekly report. 1996;45(34):729-33.
2. Follow-up on Kaposi's sarcoma and Pneumocystis pneumonia. MMWR Morbidity and mortality weekly report. 1981;30(33):409-10.
3. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. MMWR Morbidity and mortality weekly report. 1981;30(25):305-8.
4. Pneumocystis pneumonia--Los Angeles. MMWR Morbidity and mortality weekly report. 1981;30(21):250-2.
5. Broder S, Gallo RC. A pathogenic retrovirus (HTLV-III) Available at:ed to AIDS. N Engl J Med. 1984;311(20):1292-7. DOI: 10.1056/nejm198411153112006
6. Sarngadharan MG, DeVico AL, Bruch L, Schüpbach J, Gallo RC. HTLV-III: the etiologic agent of AIDS. Princess Takamatsu Symp. 1984;15:301-8.
7. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science. 1984;224(4648):497-500. DOI: 10.1126/science.6200935
8. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science. 1984;224(4648):500-3. DOI: 10.1126/science.6200936
9. Schüpbach J, Popovic M, Gilden RV, Gonda MA, Sarngadharan MG, Gallo RC. Serological analysis of a subgroup of human T-lymphotropic retroviruses (HTLV-III) associated with AIDS. Science. 1984;224(4648):503-5. DOI: 10.1126/science.6200937
10. Sarngadharan MG, Popovic M, Bruch L, Schüpbach J, Gallo RC. Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. Science. 1984;224(4648):506-8. DOI: 10.1126/science.6324345
11. Safai B, Sarngadharan MG, Groopman JE, Arnett K, Popovic M, Sliski A, et al. Seroepidemiological studies of human T-lymphotropic retrovirus type III in acquired immunodeficiency syndrome. Lancet. 1984;1(8392):1438-40. DOI: 10.1016/s0140-6736(84)91933-0
12. Montagnier L, Chermann JC, Barré-Sinoussi F, Klatzmann D, Wain-Hobson S, Alizon M, et al. Lymphadenopathy associated virus and its etiological role in AIDS. Princess Takamatsu Symp. 1984;15:319-31.
13. Montagnier L, Gruest J, Chamaret S, Dauguet C, Axler C, Guétard D, et al. Adaptation of lymphadenopathy associated virus (LAV) to replication in EBV-transformed B lymphoblastoid cell lines. Science. 1984;225(4657):63-6. DOI: 10.1126/science.6328661
14. Stevenson RW. Magic Johnson Ends His Career, Saying He Has AIDS Infection; . New York Times, Section A, Page 1: BASKETBALL;. 1991;Nov. 8.
15. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med. 1987;317(4):185-91. DOI: 10.1056/nejm198707233170401
16. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331(18):1173-80. DOI: 10.1056/nejm199411033311801
17. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;337(11):734-9. DOI: 10.1056/nejm199709113371102
18. Saag MS, Holodniy M, Kuritzkes DR, O'Brien WA, Coombs R, Poscher ME, et al. HIV viral load markers in clinical practice. Nature Med. 1996;2(6):625-9. DOI: 10.1038/nm0696-625
19. Castilla J, Del Romero J, Hernando V, Marincovich B, García S, Rodríguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr. 2005;40(1):96-101. DOI: 10.1097/01.qai.0000157389.78374.45
20. Killingley B, Pozniak A. The first once-daily single-tablet regimen for the treatment of HIV-infected patients. Drugs Today (Barc). 2007;43(7):427-42. DOI: 10.1358/dot.2007.43.7.1086178
21. Gesida. Medicamentos genéricos en el tratamiento antirretroviral. Available at: http://gesida-seimcorg/wp-content/uploads/2019/01/gesida_16_genericos_cambios_2-2-1pdf. 2018.

22. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017;390(10101):1499-510. DOI: 10.1016/s0140-6736(17)31917-7

23. Hutter G, Nowak D, Mossner M, Ganepola S, Mussig A, Allers K, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Eng J Med. 2009;360(7):692-8. DOI: 10.1056/NEJMoa0802905

24. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Eng J Med. 2011;365(6):493-505. DOI: 10.1056/NEJMoa1105243

25. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Eng J Med. 2010;363(27):2587-99. DOI: 10.1056/NEJMoa1011205

26. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. Jama. 2016;316(2):171-81. DOI: 10.1001/jama.2016.5148

27. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet. 2019;393(10189):2428-38. DOI: 10.1016/s0140-6736(19)30418-0

28. UNAIDS Report. 2019. https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf:

29. Plan Nacional sobre el Sida D.G. de Salud Pública CeICNdE. Sistema de Información sobre Nuevos Diagnósticos de VIH y Registro Nacional de Casos de Sida. ISCIII. Madrid;. Available at: en: https://wwwmscbsgobes/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/doc/InformeVIH_SIDA_2018_21112018pdf. 2018.

30. Dirección General de Salud Pública CeI. Informe de Evaluación Plan Estratégico de Prevención y Control del VIH e ITS 2013-2016. Available at: en: https://wwwmscbsgobes/ciudadanos/enfLesiones/enfTransmisibles/sida/planesEstrat/informeEvaluacion_VDweb_12Dicbre18pdf. 2018.

31. Dirección General de Salud Pública CeICNdEIdSCI. Estimación del Continuo de Atención del VIH en España, 2016. Madrid: Unidad de vigilancia del VIH y conductas de riesgo. . Available at: en: https://wwwmscbsgobes/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/doc/InformeVIH_SIDA_2018_21112018pdf. 2019.

32. UNAIDS. 90-90-90: an ambitious treatment target to help end the ADIS epidemic. Geneva, Switzerland. Availabe at: http://wwwunaidsorg/en/resources/documents/2017/90-90-90 2014.

33. Kelly SL, Wilson DP. HIV Cascade Monitoring and Simple Modeling Reveal Potential for Reductions in HIV Incidence. J Acquir Immune Defic Syndr. 2015;69(3):257-63. DOI: 10.1097/qai.0000000000000655

34. Making the end of aids real: consensus building around what we mean by "epidemic contro. UNAIDS report. 2017; Available at: https://www.unaids.org/sites/default/files/media_asset/glion_oct2017_meeting_report_en.pdf DOI:

35. Documento de consenso para el seguimiento de la infección por el VIH en relación con la reproducción, embarazo, parto y profilaxis de la transmisión vertical del niño expuesto. Available at: http://gesida-seimcorg/wp-content/uploads/2018/05/gesida_VIH_embarazopdf. 2018. DOI:

36. Bosque-Prous M, Brugal MT. [Harm reduction interventions in drug users: current situation and recommendations]. Gaceta sanitaria. 2016;30 Suppl 1:99-105. DOI: 10.1016/j.gaceta.2016.04.020

37. McCormack SM, Noseda V, Molina JM. PrEP in Europe - expectations, opportunities and barriers. J Int AIDS Soc. 2016;19(7(Suppl 6)):21103. DOI: 10.7448/ias.19.7.2110321103

38. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387(10013):53-60. DOI: 10.1016/s0140-6736(15)00056-2

39. Anonimous. New data on male circumcision and HIV prevention: policy and programme implications. WHO/UNAIDS Technical Consultation on male circumcision and HIV Prevention: research implications for policy and programming Montreux,. WHO,. 2007. Available at: 1 https://apps.who.int/iris/bitstream/handle/10665/250574/WHO-HIV-2016.05-spa.pdf;jsessionid=F1200695B013984193A97828C423C513?sequence=1

40. Spielberg F, Levine RO, Weaver M. Self-testing for HIV: a new option for HIV prevention? Lancet Infect Dis. 2004;4(10):640-6. DOI: 10.1016/s1473-3099(04)01150-8

41. Brown AE, Mohammed H, Ogaz D, Kirwan PD, Yung M, Nash SG, et al. Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)? Euro Surveill. 2017. 2017;22(25). DOI: 10.2807/1560-7917.Es.2017.22.25.30553

42. Delpech V. Elimination of HIV in the United Kingdom. Revista multidisciplinar del Sida 2018;6(14):12. 2018;Available at: http://www.revistamultidisciplinardelsida.com/download/elimination-of-hiv-in-the-united-kingdom/. DOI:

43. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. Jama. 2016;316(2):171-81. DOI: 10.1001/jama.2016.5148

44. WHO. Prevalence of HIV among adults aged 15 to 49, 2017. . Available at: https://wwwwhoint/gho/hiv/epidemic_status/prevalence/en/. 2018

45. World Health Organization. Estrategia mundial del sector de la salud contra las ITS/VIH 2016-2021. Hacia el fin de las ITS. WHO/RHR/16.09 © Available at: https://wwwwhoint/reproductivehealth/publications/rtis/ghss-stis/es/. 2016.

46. Ayerdi-Aguirrebengoa O, Vera-Garcia M, Puerta-Lopez T, Rapo-

so-Utrilla M, Rodriguez-Martin C, Del Romero-Guerrero J. To whom is HIV pre-exposure prophylaxis proposed? Enferm Infecc Microbiol Clin. 2017;35(5):299-302. DOI: 10.1016/j.eimc.2016.06.006

47. Centro Nacional de Epidemiología IdSCI, Plan Nacional sobre el Sida-SG de Promoción de la Salud y Epidemiología. Encuesta Hospitalaria de pacientes con infección por el VIH: Resultados 2016. Análisis de la evolución 2001-2016. Available at: https://wwwm-scbsgobes/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/InformeEncuestaHospitalaria2016DEFpdf. 2017.
48. Fuster-Ruiz de Apodaca MJ, Laguia A, Safreed-Harmon K, Lazarus JV, Cenoz S, Del Amo J. Assessing quality of life in people with HIV in Spain: psychometric testing of the Spanish version of WHO-QOL-HIV-BREF. Health Qual Life Outcomes. 2019;17(1):144. DOI: 10.1186/s12955-019-1208-8
49. Edelman EJ, Gordon K, Justice AC. Patient and provider-reported symptoms in the post-cART era. AIDS Behav. 2011;15(4):853-61. DOI: 10.1007/s10461-010-9706-z
50. Wilson NL, Azuero A, Vance DE, Richman JS, Moneyham LD, Raper JL, et al. Identifying Symptom Patterns in People Living With HIV Disease. J Assoc Nurses AIDS Care. 2016;27(2):121-32. DOI: 10.1016/j.jana.2015.11.009
51. Fuster-Ruiz de Apodaca MJ, Laguía A, Safreed-Harmon K, Lazarus JV, Cenoz S, Del Amo J. Assessing quality of life in people with HIV in Spain: psychometric testing of the Spanish version of WHO-QOL-HIV-BREF. Health Qual Life Outcomes. 2019;17(1):144. DOI: 10.1186/s12955-019-1208-8
52. Fuster-Ruiz de Apodaca MJ, Sánchez-Vega N, Galindo MJ, Marín-Jimenez I, de Toro J, Orozco-Beltrán D, et al. The Influence of Patient Experience with Healthcare on the Health-Related Quality of Life of People Living with HIV: An Observational Cross-Sectional Survey. Infect Dis Ther. 2019;8(3):369-82. DOI: 10.1007/s40121-019-0252-3
53. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med. 2003;26(1):1-7. DOI: 10.1207/s15324796abm2601_01
54. Luzuriaga K, Mofenson LM. Challenges in the Elimination of Pediatric HIV-1 Infection. New Engl J Med. 2016;374(8):761-70. DOI: 10.1056/NEJMra1505256
55. Peters H, Francis K, Sconza R, Horn A, C SP, Tookey PA, et al. UK Mother-to-Child HIV Transmission Rates Continue to Decline: 2012-2014. Clin infect Dis. 2017;64(4):527-8. DOI: 10.1093/cid/ciw791
56. Prieto LM, Gonzalez-Tome MI, Munoz E, Fernandez-Ibieta M, Soto B, Del Rosal T, et al. Low rates of mother-to-child transmission of HIV-1 and risk factors for infection in Spain: 2000-2007. Ped Infect Dis J. 2012;31(10):1053-8. DOI: 10.1097/INF.0b013e31826fe968
57. Mandelbrot L, Tubiana R, Le Chenadec J, Dollfus C, Faye A, Pannier E, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin infect Dis. 2015;61(11):1715-25. DOI: 10.1093/cid/civ578
58. Jiménez De Ory S, González-Tomé MI, Fernández Mcphee C. Situación De Los Pacientes VIH De Transmisión Vertical Transferidos A Unidades De Adultos (CoRISpe-FARO). Poster 112 Congreso GESIDA 2018, Madrid. 2018. DOI:
59. Guillen S, Prieto L, Jimenez de Ory S, Gonzalez-Tome MI, Rojo P, Navarro ML, et al. Prognostic factors of a lower CD4/CD8 ratio in long term viral suppression HIV infected children. PloS one. 2019;14(8):e0220552. DOI: 10.1371/journal.pone.0220552
60. de Mulder M, Yebra G, Navas A, de Jose MI, Gurbindo MD, Gonzalez-Tome MI, et al. High drug resistance prevalence among vertically HIV-infected patients transferred from pediatric care to adult units in Spain. PloS one. 2012;7(12):e52155. DOI: 10.1371/journal.pone.0052155
61. Ruiz-Saez B, García MM, de Aragon AM, Gil-Correa M, Melero H, Malpica NA, et al; Cohorte Nacional de VIH pediátrica de la RED RIS (CoRISpe), Madrid, Spain. Effects of perinatal HIV-infection on the cortical thickness and subcortical gray matter volumes in young adulthood. Medicine (Baltimore). 2021 Apr 16;100(15):e25403. doi: 10.1097/MD.0000000000025403.
62. Sainz T, Alvarez-Fuente M, Navarro ML, Diaz L, Rojo P, Blazquez D, et al. Subclinical atherosclerosis and markers of immune activation in HIV-infected children and adolescents: the CaroVIH Study. J Acquir Immune Defic Syndr. 2014;65(1):42-9. DOI: 10.1097/QAI.0b013e3182a9466a
63. Jimenez B, Sainz T, Diaz L, Mellado MJ, Navarro ML, Rojo P, et al. Low Bone Mineral Density in Vertically HIV-infected Children and Adolescents: Risk Factors and the Role of T-cell Activation and Senescence. Pediatr Infect Dis J. 2017;36(6):578-83. DOI: 10.1097/inf.0000000000001506
64. Carrasco I, Sainz Talia, Frick Marie Antoinette, et al. . Response to Direct Acting Antivirals for hepatitis C treatment in vertically HIV/HCV co-infected patients. J Viral Hepat. 2020;27(9):955-958. doi: 10.1111/jvh.13308.
65. Prieto LM, Fernandez McPhee C, Rojas P, Mazariegos D, Munoz E, Mellado MJ, et al. Pregnancy outcomes in perinatally HIV-infected young women in Madrid, Spain: 2000-2015. PloS one. 2017;12(8):e0183558. DOI: 10.1371/journal.pone.0183558
66. Cuellar-Flores I, Sainz T, Velo C, Gonzalez-Tome MI, Garcia-Navarro C, Fernandez-Mcphee C, et al. Impact of HIV on the health-related quality of life in youth with perinatally acquired HIV. World J Pediatr. 2019;15(5):492-8. DOI: 10.1007/s12519-019-00281-z
67. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143-55. DOI: 10.1016/s0140-6736(18)32462-0
68. Rodriguez-Mora S, Spivak AM, Szaniawski MA, Lopez-Huertas MR, Alcami J, Planelles V, et al. Tyrosine Kinase Inhibition: a New Perspective in the Fight against HIV. Current HIV/AIDS reports. 2019;16(5):414-22. DOI: 10.1007/s11904-019-00462-5
69. Suarez-Garcia I, Gonzalez J, Berenguer J, Garcia F, Portilla J, Muga R, et al. Reasons for noncompliance with the national guidelines for initial antiretroviral therapy of HIV-infected patients in Spain, 2010-2015. Enferm Infecc Microbiol Clin. 20192019;37(9):580-7.

DOI: 10.1016/j.eimc.2019.02.007

70. Suarez-Garcia I, Ruiz-Alguero M, Garcia Yubero C, Moreno C, Belza MJ, Estebanez M, et al. Physicians' opinions on generic antiretroviral drugs and single-tablet regimen de-simplification for the treatment of HIV infection: a multicentre survey in Spain. J Antimicrob Chemother. 2020;75(2):466-72. DOI: 10.1093/jac/dkz439
71. Tarancon-Diez L, Rodriguez-Gallego E, Rull A, Peraire J, Vilades C, Portilla I, et al. Immunometabolism is a key factor for the persistent spontaneous elite control of HIV-1 infection. EBioMedicine. 2019;42:86-96. DOI: 10.1016/j.ebiom.2019.03.004
72. Centro Nacional de Epidemiología – Instituto de Salud Carlos III. Unidad de vigilancia del VIH y conductas de riesgo. Estimación del Continuo de Atención del VIH en España, 2016. Madrid: / Plan Nacional sobre el sida – Dirección General de Salud Pública, Calidad e Innovación; 2019 . Available at: -> https://wwwisciiies/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/VIH/INFORMES%20ESPECIALES/ESTIMACION_DEL_CONTINUO_DE_ATENCION_DEL_VIH_EN_ESPANA_2019pdf
73. Dirección General de Salud Pública CeICNdEldSCI. Estimación del continuo de atención del VIH en España, 2016. Available at: https://wwwmscbsgobes/ciudadanos/enfLesiones/enfTransmisibles/sida/docs/ESTIMACION_DEL_CONTINUO_DE_ATENCION_DEL_VIH_EN_ESPANApdf.
74. Schackman BR, Gebo KA, Walensky RP, Losina E, Muccio T, Sax PE, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care. 2006;44(11):990-7. DOI: 10.1097/01.mlr.0000228021.89490.2a
75. Ruiz.-Algueró M, Suárez-García I, Alvarez-del Arco D, Lázaro P, Moreno S, Jarrín I, et al. Uso de recursos sanitarios y costes asociados al tratamiento antirretroviral de primera línea en España en la era de los inhibidores de la integrasa. Available at https://wwwpharmcareespcom/indexphp/PharmaCARE/article/view/500.
76. Documento de consenso de GESIDA/Plan nacional sobre el SIDA respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. Available at: http://gesida-seimcorg/wp-content/uploads/2018/01/gesida_TAR_adultos_v3-1pdf.
77. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;372(9635):293-9. DOI: 10.1016/s0140-6736(08)61113-7
78. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med. 2007;146(2):87-95. DOI: 10.7326/0003-4819-146-2-200701160-00003
79. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L. Ann Intern Med. 2003;139(10):810-6. DOI: 10.7326/0003-4819-139-10-200311180-00008
80. Ramiro MA, Llibre JM. Legal, ethical, and economic implications of breaking down once-daily fixed-dose antiretroviral combinations into their single components for cost reduction. Enferm Infecc Microbiol Clin. 2014;32(9):598-602. DOI: 10.1016/j.eimc.2013.06.008
81. Kumarasamy N, Solomon S, Chaguturu SK, Cecelia AJ, Vallabhaneni S, Flanigan TP, et al. The changing natural history of HIV disease: before and after the introduction of generic antiretroviral therapy in southern India. Clin Infect Dis. 2005;41(10):1525-8. DOI: 10.1086/497267
82. Gesida. Plan nacional sobre el sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. 2019.
83. Gesida. Panel de expertos de GeSIDA y Plan Nacional sobre el Sida. Documento de consenso de GeSIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2019). Available at: http://gesida-seimcorg/wp-content/uploads/2019/01/gesida_DC_TAR_2019_v_finalpdf.
84. GeSida y Plan Nacional. Panel de expertos de GeSIDA y Plan Nacional sobre el SIDA. Documento de consenso de GeSIDA/Plan Nacional sobre el SIDA respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. Available at:http://gesida-seimcorg/wp-content/uploads/2019/02/Guia_Tar_Gesida_Ene_2019pdf.
85. Walensky RP, Sax PE, Nakamura YM, Weinstein MC, Pei PP, Freedberg KA, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. Ann Intern Med. 2013;158(2):84-92. DOI: 10.7326/0003-4819-158-2-201301150-00002
86. Papot E, Landman R, Louni F, Charpentier C, Peytavin G, Certain A, et al. Budget impact of antiretroviral therapy in a French clinic cohort. AIDS. 2017;31(9):1271-9. DOI: 10.1097/qad.0000000000001467
87. Llibre JM, Arribas JR, Domingo P, Gatell JM, Lozano F, Santos JR, et al. Clinical implications of fixed-dose coformulations of antiretrovirals on the outcome of HIV-1 therapy. AIDS. 2011;25(14):1683-90. DOI: 10.1097/QAD.0b013e3283499cd9
88. Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIV. BMJ open. 2013;3(8). DOI: 10.1136/bmjopen-2013-003028
89. Sax PE, Meyers JL, Mugavero M, Davis KL. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. PloS one. 2012;7(2):e31591. DOI: 10.1371/journal.pone.0031591
90. Ramjan R, Calmy A, Vitoria M, Mills EJ, Hill A, Cooke G, et al. Systematic review and meta-analysis: Patient and programme impact of fixed-dose combination antiretroviral therapy. Trop Med Int Health. 2014;19(5):501-13. DOI: 10.1111/tmi.12297
91. Clay PG, Nag S, Graham CM, Narayanan S. Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens. Medicine. 2015;94(42):e1677. DOI: 10.1097/md.0000000000001677
92. Llibre JM, de Lazzari E, Molina JM, Gallien S, Gonzalez-Garcia J, Imaz A, et al. Cost-effectiveness of initial antiretroviral treat-

ment administered as single vs. multiple tablet regimens with the same or different components. Enferm Infecc Microbiol Clin. 2018;36(1):16-20. DOI: 10.1016/j.eimc.2016.07.006

93. Engsig FN, Gerstoft J, Helleberg M, Nielsen LN, Kronborg G, Mathiesen LR, et al. Effectiveness of antiretroviral therapy in individuals who for economic reasons were switched from a once-daily single-tablet regimen to a triple-tablet regimen. J Acquir Immune Defic Syndr. 2014;66(4):407-13. DOI: 10.1097/qai.0000000000000199
94. Beck EJ, Mandalia S, Sangha R, Youle M, Brettle R, Gompels M, et al. Lower healthcare costs associated with the use of a single-pill ARV regimen in the UK, 2004-2008. PloS one. 2012;7(10):e47376. DOI: 10.1371/journal.pone.0047376
95. Homar F, Lozano V, Martinez-Gomez J, Oyaguez I, Pareja A, Payeras A, et al. Cost analysis of HIV treatment and drug-related adverse events when fixed-dose combinations of antiretrovirals (FDCs) were stopped, versus continuation with FDCs. Health Econ Rev. 2012;2(1):16. DOI: 10.1186/2191-1991-2-16
96. Rossi MC, Inojosa WO, Battistella G, Carniato A, Farina F, Giobbia M, et al. Desimplification to multi-tablet antiretroviral regimens in human immunodeficiency virus-type 1 infected adults: A cohort study. World J Clin Cases.2019;7(14):1814-24. DOI: 10.12998/wjcc.v7.i14.1814
97. Krentz HB, Campbell S, Lahl M, Gill MJ. De-simplifying single-tablet antiretroviral treatments: uptake, risks and cost savings. HIV Med. 2019;20(3):214-21. DOI: 10.1111/hiv.12701
98. Olalla J, Perez-Stachowski J, Tortajada B, Del Arco A, Marquez E, De la Torre J, et al. Efficacy and safety of the switch of Triumeq(R) to generic (abacavir + lamivudine) + Tivicay(R): data at 24 weeks. BMC Pharmacol Toxicol. 2018;19(1):63. DOI: 10.1186/s40360-018-0252-z
99. Gesida. Panel de expertos de GeSIDA y Plan Nacional sobre el Sida. Medicamentos genéricos en el tratamiento antirretroviral. 2019
100. (EACS) EACS. Guidelines Version 10.0 November. Available at: https://wwweacsocietyorg/files/2019_guidelines-100_finalpdf.
101. Leon A, Perez I, Ruiz-Mateos E, Benito JM, Leal M, Lopez-Galindez C, et al. Rate and predictors of progression in elite and viremic HIV-1 controllers. AIDS. 2016;30(8):1209-20. DOI: 10.1097/qad.0000000000001050
102. Crowell TA, Gebo KA, Blankson JN, Korthuis PT, Yehia BR, Rutstein RM, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. J Infect Dis. 2015;211(11):1692-702. DOI: 10.1093/infdis/jiu809
103. Crowell TA, Ganesan A, Berry SA, Deiss RG, Agan BK, Okulicz JF. Hospitalizations among HIV controllers and persons with medically controlled HIV in the U.S. Military HIV Natural History Study. J Int AIDS Soc. 2016;19(1):20524. DOI: 10.7448/ias.19.1.20524
104. Dominguez-Molina B, Leon A, Rodriguez C, Benito JM, Lopez-Galindez C, Garcia F, et al. Analysis of Non-AIDS-Defining Events in HIV Controllers. Clin Infect Dise. 2016;62(10):1304-9. DOI: 10.1093/cid/ciw120
105. Pernas M, Tarancon-Diez L, Rodriguez-Gallego E, Gomez J, Prado JG, Casado C, et al. Factors Leading to the Loss of Natural Elite Control of HIV-1 Infection. J Virol. 2018;92(5). DOI: 10.1128/jvi.01805-17
106. Chereau F, Madec Y, Sabin C, Obel N, Ruiz-Mateos E, Chrysos G, et al. Impact of CD4 and CD8 dynamics and viral rebounds on loss of virological control in HIV controllers. PloS one. 2017;12(4):e0173893. DOI: 10.1371/journal.pone.0173893
107. Canoui E, Lecuroux C, Avettand-Fenoel V, Gousset M, Rouzioux C, Saez-Cirion A, et al. A Subset of Extreme Human Immunodeficiency Virus (HIV) Controllers Is Characterized by a Small HIV Blood Reservoir and a Weak T-Cell Activation Level. Open Forum Infect Dis. 2017;4(2):ofx064. DOI: 10.1093/ofid/ofx064
108. Li JZ, Segal FP, Bosch RJ, Lalama CM, Roberts-Toler C, Delagreverie H, et al. ART reduces T cell activation and immune exhaustion markers in HIV controllers. Clin Infect Dis. 2019. DOI: 10.1093/cid/ciz442
109. UN Joint Programme on HIV/AIDS (UNAIDS), The Gap Report, 2014, available at: https://www.refworld.org/docid/53f1e1604.html [accessed 11 March 2020] The Gap Report. 2014.
110. Deeks SG, Lewin SR, Ross AL, Ananworanich J, Benkirane M, Cannon P, et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. Nature Med. 2016;22(8):839-50. DOI: 10.1038/nm.4108
111. Tebas P, Stein D, Tang WW, Frank I, Wang SQ, Lee G, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. New Engl J Med. 2014;370(10):901-10. DOI: 10.1056/NEJMoa1300662
112. Gupta RK, Abdul-Jawad S, McCoy LE, Mok HP, Peppa D, Salgado M, et al. HIV-1 remission following CCR5Delta32/Delta32 haematopoietic stem-cell transplantation. Nature. 2019;568(7751):244-8. DOI: 10.1038/s41586-019-1027-4
113. Fauci AS, Folkers GK, Marston HD. Ending the global HIV/AIDS pandemic: the critical role of an HIV vaccine. Clin Infect Dis. 2014;59 Suppl 2:S80-4. DOI: 10.1093/cid/ciu420
114. Hemelaar J, Gouws E, Ghys PD, Osmanov S. Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004. AIDS. 2006;20(16):W13-23. DOI: 10.1097/01.aids.0000247564.73009.bc
115. McCoy LE, Burton DR. Identification and specificity of broadly neutralizing antibodies against HIV. Immunol Rev. 2017;275(1):11-20. DOI: 10.1111/imr.12484
116. Pegu A, Borate B, Huang Y, Pauthner MG, Hessell AJ, Julg B, et al. A Meta-analysis of Passive Immunization Studies Shows that Serum-Neutralizing Antibody Titer Associates with Protection against SHIV Challenge. Cell Host Microbe. 2019;26(3):336-46.e3. DOI: 10.1016/j.chom.2019.08.014
117. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. New Engl J Med. 2009;361(23):2209-20. DOI: 10.1056/NEJMoa0908492
118. Barouch DH, O'Brien KL, Simmons NL, King SL, Abbink P, Maxfield LF, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. Nature Med. 2010;16(3):319-23. DOI: 10.1038/nm.2089
119. Kawashima Y, Pfafferott K, Frater J, Matthews P, Payne R, Addo

M, et al. Adaptation of HIV-1 to human leukocyte antigen class I. Nature. 2009;458(7238):641-5. DOI: 10.1038/nature07746

120. Mothe B, Llano A, Ibarrondo J, Daniels M, Miranda C, Zamarreno J, et al. Definition of the viral targets of protective HIV-1-specific T cell responses. J Transl Med. 2011;9:208. DOI: 10.1186/1479-5876-9-208
121. Letourneau S, Im EJ, Mashishi T, Brereton C, Bridgeman A, Yang H, et al. Design and pre-clinical evaluation of a universal HIV-1 vaccine. PloS one. 2007;2(10):e984. DOI: 10.1371/journal.pone.0000984
122. Shan L, Deng K, Shroff NS, Durand CM, Rabi SA, Yang HC, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity. 2012;36(3):491-501. DOI: 10.1016/j.immuni.2012.01.014
123. Organization WH. WHO. WHO expands recommendation on oral pre-exposure prophylaxis of VIH infection (PrEP). 2015;(November). refere. 2015;Available at: at https://www.who.int/hiv/pub/prep/policy-brief-prep-2015/en/(WHO reference number: WHO/HIV/2015.48):2.
124. European AIDS Clinical Society (EACS). Guía Clínica Versión 9 Octubre de 2017. Eur AIDS Clin Soc. Available at: - https://wwweacsocietyorg/files/guidlines-90-spanishpdf.
125. Moreno S, Antela A, Garcia F, Del Amo J, Boix V, Coll P, et al. Executive summary: Pre-exposure prophylaxis for prevention of HIV infection in adults in Spain: July 2016. nferm Infecc Microbiol Clin.. 2017;35(6):377-83. DOI: 10.1016/j.eimc.2016.11.016
126. López López MT dMJF, Alonso Bedate C, Bellver Capella V, Cadena Serrano F, de los Reyes López M, et al. . Informe del Comité de Bioética de España sobre la financiación pública del medicamento Profilaxis preexposición en la prevencion del VIH (PrEP). Available at: http://assetscomitedebioeticaes/files/documentacion/es/Informe_PrEPpdf.
127. Chloe Orkin. Long-acting cabotegravir + rilpivirine for HIV maintenance: flair week 48 results. Available at: http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-hiv-maintenance-flair-week-48-results.
128. Susan Swindells. Long-acting cabotegravir + rilpivirine for HIV maintenance: flair week 48 results. Available at: http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-maintenance-therapy-atlas-week-48-results.
129. Efficacy, Safety and Tolerability Study of Long-acting Cabotegravir Plus Long-acting Rilpivirine (CAB LA + RPV LA) in Human-immunodeficiency Virus-1 (HIV-1) Infected Adults. US National Library of Medicine, ClinicalTrialsgov. 2019; Available at: https://clinicaltrials.gov/ct2/show/NCT03299049.
130. Teichner P ea. Patient Adherence to Long-Acting Injectable Cabotegravir + Rilpivirine Through 48 Weeks of Maintenance Therapy in the Phase 3 ATLAS and FLAIR Studies. Open Forum Infect Dis. 2019; Oct; 6(Suppl 2): S20. DOI: 10.1093/ofid/ofz359.043
131. Garris C. Perceptions of and Preferences for Oral or Long-Acting Injectable Antiretroviral Treatment Regimens in the United States and Canada. Open Forum Infect Dis. 2019 Oct; 6(Suppl 2): S866–S867. doi: 10.1093/ofid/ofz360.2177
132. Daar Eea. Safety and Antiviral Activity Over 10 Days Following a Single Dose of Subcutaneous GS-6207, a First-in-Class, Long-Acting HIV Capsid Inhibitor in People Living With HIV. Presented at 10th IAS Conference on HIV Science, 21–24 July . Available at: https://onlinelibrarywileycom/doi/101002/jia225327.
133. Stephen R Y. In Vitro Resistance Profile of GS-6207, a First-in-Class Picomolar HIV Capsid Inhibitor in Clinical Development as a Novel Long-Acting Antiretroviral Agent. Available at: http://wwwnataporg/2019/IAS/IAS_70htm.
134. Glober JA. CROI, Boston, MA. Abst 437LB. Available at: https://wwwiasusaorg/wp-content/uploads/2016/06/24-e1-4pdf.
135. Pegu A. Trispecific antibodies for prevention and treatment of hiv-1 infection. Available at:http://www.croiconference.org/sessions/trispecific-antibodies-prevention-and-treatment-hiv-1-infection. 2018.
136. Pulido F, Matarranz M, Rodriguez-Rivera V, Fiorante S, Hernando A. Boosted protease inhibitor monotherapy. What have we learnt after seven years of research? AIDS Rev. 2010;12(3):127-34.
137. Mathis S, Khanlari B, Pulido F, Schechter M, Negredo E, Nelson M, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. PloS one. 2011;6(7):e22003. DOI: 10.1371/journal.pone.0022003
138. Moreno S, Perno CF, Mallon PW, Behrens G, Corbeau P, Routy JP, et al. Two-drug vs. three-drug combinations for HIV-1: Do we have enough data to make the switch? HIV Med. 2019;20 Suppl 4:2-12. DOI: 10.1111/hiv.12716
139. Perez-Molina JA, Pulido F, Di Giambenedetto S, Ribera E, Moreno S, Zamora J, et al. Individual patient data meta-analysis of randomized controlled trials of dual therapy with a boosted PI plus lamivudine for maintenance of virological suppression: GeSIDA study 9717. J Antimicrob Chemother. 2018;73(11):2927-35. DOI: 10.1093/jac/dky299
140. Aboud M, Orkin C, Podzamczer D, Bogner JR, Baker D, Khuong-Josses MA, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. Lancet HIV. 2019;6(9):e576-e87. DOI: 10.1016/s2352-3018(19)30149-3
141. Puronen CE, Ford ES, Uldrick TS. Immunotherapy in People With HIV and Cancer. Front Immunol. 2019;10:2060. DOI: 10.3389/fimmu.2019.02060
142. Brady JM, Baltimore D, Balazs AB. Antibody gene transfer with adeno-associated viral vectors as a method for HIV prevention. Immunol Rev. 2017;275(1):324-33. DOI: 10.1111/imr.12478
143. Mouquet H. Antibody B cell responses in HIV-1 infection. Trends Immunol. 2014;35(11):549-61. DOI: 10.1016/j.it.2014.08.007
144. Caskey M, Klein F, Lorenzi JC, Seaman MS, West AP, Jr., Buckley N, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature. 2015;522(7557):487-91. DOI: 10.1038/nature14411
145. Bar KJ, Sneller MC, Harrison LJ, Justement JS, Overton ET, Petrone ME, et al. Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. New Engl J Med. 2016;375(21):2037-50. DOI: 10.1056/NEJMoa1608243

146. Caskey M, Schoofs T, Gruell H, Settler A, Karagounis T, Kreider EF, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. Nature Med. 2017;23(2):185-91. DOI: 10.1038/nm.4268

147. Mendoza P, Gruell H, Nogueira L, Pai JA, Butler AL, Millard K, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature. 2018;561(7724):479-84. DOI: 10.1038/s41586-018-0531-2

148. Bar-On Y, Gruell H, Schoofs T, Pai JA, Nogueira L, Butler AL, et al. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. Nature Med. 2018;24(11):1701-7. DOI: 10.1038/s41591-018-0186-4

149. Rappuoli R, Bottomley MJ, D'Oro U, Finco O, De Gregorio E. Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design. J Exp Med. 2016;213(4):469-81. DOI: 10.1084/jem.20151960

150. Banga R, Procopio FA, Noto A, Pollakis G, Cavassini M, Ohmiti K, et al. PD-1(+) and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals. Nature Med. 2016;22(7):754-61. DOI: 10.1038/nm.4113

151. Fromentin R, DaFonseca S, Costiniuk CT, El-Far M, Procopio FA, Hecht FM, et al. PD-1 blockade potentiates HIV latency reversal ex vivo in CD4(+) T cells from ART-suppressed individuals. Nat Commun. 2019;10(1):814. DOI: 10.1038/s41467-019-08798-7

152. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. New Engl J Med. 2012;366(26):2455-65. DOI: 10.1056/NEJMoa1200694

153. Hogan LE, Vasquez J, Hobbs KS, Hanhauser E, Aguilar-Rodriguez B, Hussien R, et al. Increased HIV-1 transcriptional activity and infectious burden in peripheral blood and gut-associated CD4+ T cells expressing CD30. PLoS pathogens. 2018;14(2):e1006856. DOI: 10.1371/journal.ppat.1006856

154. Garrido C, Abad-Fernandez M, Tuyishime M, Pollara JJ, Ferrari G, Soriano-Sarabia N, et al. Interleukin-15-Stimulated Natural Killer Cells Clear HIV-1-Infected Cells following Latency Reversal Ex Vivo. J Virol. 2018;92(12). DOI: 10.1128/jvi.00235-18

155. Coiras M, Ambrosioni J, Cervantes F, Miro JM, Alcami J. Tyrosine kinase inhibitors: potential use and safety considerations in HIV-1 infection. Expert Opin Drug Saf. 2017;16(5):547-59. DOI: 10.1080/14740338.2017.1313224

156. Bermejo M, Ambrosioni J, Bautista G, Climent N, Mateos E, Rovira C, et al. Evaluation of resistance to HIV-1 infection ex vivo of PBMCs isolated from patients with chronic myeloid leukemia treated with different tyrosine kinase inhibitors. Biochem Pharmacol. 2018;156:248-64. DOI: 10.1016/j.bcp.2018.08.031

157. Lazarus JV, Barton SE, Bernardino JI. Taking the long-view in a personalised approach to HIV care. Lancet HIV. 2017;4(11):e483-e5. DOI: 10.1016/s2352-3018(17)30182-0

158. SI-health. Descripción del modelo óptimo de atención al paciente VIH. SI-health. Available at: https://viivhealthcarecom/content/dam/cf-viiv/viiv-healthcare/es_ES/documents/Modelo%20%C3%B3ptimo%20atenci%C3%B3n%20VIHpdf.

159. Ministerio de Sanidad SSeI. Guía de Recomendaciones para el diagnóstico Precoz del VIH en el ámbito sanitario 2014; Available at: - http://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/docs/GUIA_DX_VIH.pdf

160. Sullivan PS ea. The Impact of Pre-exposure Prophylaxis With FTC/TDF on HIV Diagnoses, 2012-2016, United States, 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, the Netherlands. 2018;Available at: http://www.natap.org/2018/IAC/IAC_17.htm(Conference

161. Ministerio de Sanidad CyBS. Plan Nacional sobre el SIDA. Pacto social por la no discriminación y la igualdad de trato asociada al VIH, 2018. Available at: https://wwwomsidaorg/wp-content/uploads/2018/11/PACTO-SOCIAL-2018pdf.

Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/094.2021

Carlos Avellaneda Martínez[1]
Julio César Santos Pastor[2]
Isabel María Marcos Sánchez[1]
Ainhoa Narros Giménez[1]
María Gutiérrez de Antón[1]
Pablo Alonso Chacón[1]

Prevalencia de infección por SARS-CoV-2 durante la primera oleada de la pandemia entre personal sanitario y no sanitario del Hospital General de Segovia, Castilla y León

[1]Servicio de Urgencias. Hospital General de Segovia. España.
[2]Centro de Salud, Segovia Rural. Segovia. España

Article history
Received:25 June 2021; Revision Requested: 8 September 2021; Revision Received: 25 October 2021; Accepted: 15 November 2021; Published: 17 January 2022

RESUMEN

Introducción. Los trabajadores sanitarios y no sanitarios (TSyNS) de un hospital están más expuestos al contagio por SARS-CoV-2 que la población general. Estudiamos la prevalencia de esta infección en los trabajadores del hospital de Segovia tras la primera ola.-

Material y métodos. Estudio monocéntrico, observacional, transversal, realizado entre el 29 de abril y el 14 de mayo de 2020. Se diagnosticó la infección mediante test de inmunocromatografía capilar para anticuerpos IgG y/o IgM, o PCR. Se estudiaron variables laborales, de salud, y de exposición.

Resultados. Participaron en el estudio 1.335 TSyNS de un total 1.667 (80,1%), un 79,3% mujeres, con una edad media de 47,3 años, y de 47,1 para los hombres. La prevalencia de infectados fue del 21,95%, el 24,7% asintomáticos. La edad presentó una OR significativa de 1,02/año. La exposición extralaboral aumentó la prevalencia un 16,8%. El uso continuado del Equipo de Protección Individual (EPI) y la administración de nebulizaciones presentaron una OR de 0,54 y 0,46 respectivamente. Los síntomas asociados a mayor prevalencia fueron anosmia (OR 9,31), ageusia (OR 3,05), y fiebre (OR 1,94). Hasta la fecha, el 75% de los TSyTNS infectados lo hicieron en la primera ola.

Conclusiones. La prevalencia es mayor entre los TSyNS que en la población general. La edad se asocia a una mayor prevalencia de infección. Casi un 25% de los infectados fue asintomático. El uso de EPI de forma continuada se asoció a menor prevalencia. Los síntomas con mayor asociación fueron fiebre, anosmia, y ageusia.

Palabras clave: Infección por coronavirus, prevalencia, estudio transversal, personal hospitalario, factores de riesgo.

Correspondencia:
Julio César Santos Pastor
Hospital General de Segovia.
C/ Luis Erik Clavería Neurólogo S/N. 40002. Segovia. España.
E-mail: jsantosp@saludcastillayleon.es

Prevalence of SARS-CoV-2 infection during the first wave of the pandemic among health and non-health personnel of the General Hospital of Segovia, Castilla y León

ABSTRACT

Introduction. Health and non-health workers (H&NH-W) in a hospital are more exposed to SARS-CoV-2 infection than the general population. We studied the prevalence of this infection in these workers of Segovia´s Hospital after the first epidemic wave.

Material and methods. Monocentric, observational, cross-sectional study, carried out between April 29 and May 14, 2020. The infection was diagnosed by capillary immunochromatography test for IgG and / or IgM antibodies, or PCR. Work, health, and exposure variables were studied.

Results. A total of 1,335 H&NH-W participated in the study out of a total of 1,667 (80.1%), 79.3% women, with a mean age of 47.3 years, and 47.1 for men. The prevalence of infected was 21.95%, 24.7% asymptomatic. Age presented a significant OR of 1.02/year. Exposure outside of work increased the prevalence by 16.8%. The continued use of Personal Protective Equipment (PPE) and the administration of nebulizations presented an OR of 0.54 and 0.46 respectively. The symptoms associated with the highest prevalence were anosmia (OR 9.31), ageusia (OR 3.05), and fever (OR 1.94). Today, about 75% of H&NH-W were infected in the first wave.

Conclusions. The prevalence is higher among healthcare workers than the population they serve. Age is associated with a higher prevalence of infection. Almost a quarter of those infected were asymptomatic. The continuous use of PPE was associated with a lower prevalence, for that the administration of nebulisations could be safe. The symptoms with the greatest association were fever, anosmia, and ageusia.

Keywords: Coronavirus Infections, Prevalence, Cross-Sectional Studies, Hospital Personnel, Risk Factors

INTRODUCCIÓN

Hasta el 8 de septiembre de 2020, España era uno de los países europeos más severamente afectados por la COVID-19, con más de 525,000 casos confirmados, y más de 29.000 muertes [1]. Hasta el 21 de mayo de 2020 se habían notificado a la Red Nacional de Vigilancia Epidemiológica (RENAVE) 40.921 casos de COVID-19 en personal sanitario con diagnóstico previo al 11 de mayo de 2020, lo que suponía un 24,1% del total de casos de COVID-19 declarados a la RENAVE hasta esa fecha [2].

Los datos publicados en RENAVE son los declarados, y no tienen en cuenta los casos de trabajadores infectados asintomáticos que no solicitaron asistencia sanitaria, o que no fueron sometidos a una prueba diagnóstica en un momento, el del inicio de la pandemia, de escasez de las mismas.

Nuestro estudio pretende conocer cuál fue la prevalencia real de infección por SARS-CoV-2 inmediatamente tras la primera onda epidémica entre los trabajadores sanitarios y no sanitarios (TSyNS) del Hospital General de Segovia, en Castilla y León, e investigar su posible relación con factores laborales, de salud, y de exposición, y encontrar los síntomas asociados a una mayor prevalencia.

Para ello se ofreció a la totalidad de trabajadores del centro sanitario una prueba de detección de anticuerpos mediante inmunocromatografía capilar (la única prueba de detección de anticuerpos disponible en aquel momento), además de considerar el resultado de pruebas diagnósticas previas si las había (inmunocromatografía o PCR).

MATERIAL Y MÉTODOS

Sujetos y diseño del estudio. Estudio monocéntrico, observacional, transversal, diseñado y realizado en el Hospital General de Segovia (HGS), con 375 camas y 1.667 TSyNS, que da cobertura a la totalidad de la población de la provincia: 153.478 habitantes (76.445 mujeres y 77.033 hombres) según censo del 1 de enero de 2020 [3]. El estudio fue aprobado por el Comité de Ética e Investigación (CEIm) de la Gerencia de Asistencia Sanitaria de Segovia en abril 2020.

Durante el período de 29 de abril a 14 de mayo de 2020 el Servicio de Medicina Preventiva ofreció a la totalidad de los TSyNS del Hospital General de Segovia la realización de una prueba rápida de detección de anticuerpos en suero o sangre total contra el SARS-CoV-2.

Durante la extracción se invitó a la participación voluntaria en el estudio, y a aquellos que aceptaron se les entregó un cuestionario y se les solicitó consentimiento para el acceso a su historial clínico con el fin de poder recoger el resultado final de esta prueba y de las que se hubieran realizado con anterioridad.

Cuestionario. Las variables estudiadas fueron género, edad, categoría profesional, servicio donde desempeñaba sus funciones, duración de la jornada laboral, patología previa conocida, síntomas que sugirieran infección por coronavirus, grupo sanguíneo y grupo Rh, tareas realizadas habitualmente en su puesto de trabajo, pruebas diagnósticas previas y su resultado, y contacto extralaboral con sujetos infectados.

Dentro de la patología previa se preguntó por hipertensión arterial (HTA), diabetes, cardiopatía isquémica, hipercolesterolemia, enfermedad pulmonar obstructiva crónica (EPOC), inmunodepresión, y obesidad.

Entre las tareas desempeñadas se preguntó si se había realizado: anamnesis y exploración física, administración de medicación nebulizada, administración de oxígeno a alto flujo, intubación orotraqueal, manejo del paciente (como puede ser ayuda en su movilidad o traslado), o alguna otra tarea que implicara contacto con el paciente o sus muestras clínicas.

Los síntomas que se recogieron fueron fiebre, mialgias, tos, dolor de garganta, dolor de cabeza, pérdida de olfato (anosmia), pérdida de gusto (ageusia), sensación de mareo, y diarrea.

Test de anticuerpos. Las muestras de sangre se obtuvieron mediante venopunción. La detección de anticuerpos (Ac) IgG o IgM se realizó en el suero empleando un kit basado en la técnica cualitativa de inmunocromatografía capilar (Diagnostic Kit for IgM/IgG Antibody to Coronavirus (SARS-CoV-2) (Lateral Flow), Livzon). La sensibilidad y especificidad combinada del test declarada por el fabricante es del 90,6 y 99,2% respectivamente [4], y las halladas mediante validación independiente por la FDA del 86.7% (IC 95% 70.3-94.7%), y 97.5% (IC 95% 91.3-99.3%) [5]: La interpretación de la prueba se realizó de forma visual por el personal del laboratorio ajena por completo a la información clínica del sujeto.

Determinación del trabajador como infectado. Se consideró trabajador infectado a todo aquel con un resultado positivo en la prueba de Livzon, o en alguna prueba anterior: inmunocromatografía para Ac IgG/M, o reacción en cadena de la polimerasa (PCR). En la Tabla 1 se muestran los distintos patrones de resultado entre los sujetos considerados como infectados.

Recogida de datos y análisis estadístico. El registro de los datos se realizó en LibreOfficeCalc v6.4.2.2 [6], y el análisis estadístico mediante el programa Epidat v4.2 [7]. Las medias se muestran junto a sus desviaciones estándard (DE), y las proporciones junto a sus intervalos de confianza al 95% (IC95%). La asociación entre la prevalencia y las variables de edad, género, variables de salud, y de exposición laboral y extralaboral, se estableció mediante un modelo de regresión logística que las incluía a todas ellas. El modelo de regresión logística para asociación de prevalencia y síntomas se ajustó según edad y género. El modelo para la asociación con grupo sanguíneo y Rh se ajustó según éstos, la edad y el género.

RESULTADOS

Sobre un total de 1.667 TSyNS se presentaron a la prueba de detección de anticuerpos 1.638 (98,2%), y de ellos 1.335 se

Tabla 1 **Resultado de las pruebas practicadas en los casos considerados infectados**

Pruebas previas al estudio		Estudio			
PCR	Ac totales[a]	Ac IgM	Ac IgG	Número	% del total
Indeterminado		(+)	(+)	3	1,02 %
(-)	(-)	(+)	(+)	2	0,68 %
(-)	(+)	(-)	(-)	3	1,02 %
(-)	(+)	(+)	(+)	5	1,71 %
(-)		(-)	(+)	15	5,12 %
(-)		(+)	(-)	2	0,68 %
(-)		(+)	(+)	31	10,58 %
(+)	(-)	(-)	(-)	1	0,34 %
(+)	(-)	(+)	(+)	2	0,68 %
(+)		(-)	(-)	26	8,87 %
(+)		(-)	(+)	37	12,63 %
(+)		(+)	(-)	8	2,73 %
(+)		(+)	(+)	75	25,60 %
(+)				1	0,34 %
	(-)	(-)	(+)	1	0,34 %
	(+)	(-)	(-)	1	0,34 %
		(-)	(+)	22	7,51 %
		(+)	(-)	20	6,83 %
		(+)	(+)	38	12,97 %
Total				**293**	**100,00 %**

[a]**Inmunocromatografía capilar IgG-M**

prestaron a colaborar en nuestro estudio y firmaron el consentimiento informado (80,1% del total de trabajadores). El 79,3% de los participantes en el estudio fueron mujeres (Tabla 2), y las edades estuvieron comprendidas entre los 20 y 69 años. La edad media fue respectivamente de 47,3 (DE 12) años para las mujeres, y 47,1 (DE 12,02) para los hombres.

Entre los 1.335 participantes en 20 (1,5%) no pudo obtenerse el resultado de pruebas diagnósticas previas. De los 1315 restantes a 510 (38,78%) se les había realizado al menos una prueba diagnóstica previa: PCR a 453 (34,45%), inmunocromatografía capilar para IgG-M a 22 (1,67%), y ambas a 35 (2,66%).

Casi el 9% de los participantes con PCR positiva previa mostraron un resultado negativo en las pruebas rápidas de anticuerpos. Este descenso concuerda con lo publicado: un 7 y 14% a las 3 y 6 semanas de infección respectivamente [8], incluso cuando la detección de anticuerpos se realiza mediante quimioluminiscencia [9].

Se detectó infección por SARS-CoV-2 en 293 trabajadores, lo que supone una prevalencia del 21,95% (IC95% 19,75-24,27), un 24,74% de ellos asintomáticos (IC95% 19,89-30,12) y que por tanto no fueron casos declarados a RENAVE.

La prevalencia fue del 23.9% entre los trabajadores que prestaron atención directa a pacientes con COVID-19 (médico/o, enfermero/a, TCAE, celador/a, y técnico/a de radiodiagnóstico), y del 16,8% en el resto (diferencia del 7,1% IC 95% 2,4-11,8%, p 0.003).

La edad presentó asociación con una mayor prevalencia de infección, con una OR ajustada de 1,02/año (IC 95% 1,01-1,04, p 0,006).

Las diferencias observadas en la prevalencia de infección según el género, la categoría profesional, el servicio, las horas de trabajo semanales, o los factores de salud individuales no presentaron significación estadística (Tabla 2). Aún así, las categorías profesionales con una mayor prevalencia fueron la de Técnicos en Cuidados Auxiliares de Enfermería (TCAE), Médicos Internos Residentes (MIR), y el Personal de limpieza.

El porcentaje de infectados fue menor entre los que declararon usar el EPI siempre (OR 0,54, IC 95% 0,29-0,99, p 0,047), y entre los que administraron tratamiento nebulizado (OR 0,46, IC95% 0,26-0,82, p 0,008).

Tabla 2 **Prevalencia de trabajadores infectados**

	Infectados (total)	% de la muestra	% de infectados (IC 95%)	OR[a] (IC 95%)	p
Género					
Mujer	237 (1059)	79,33 %	22,38 % (19,9-25,01)	0,91 (0,60-1,37)	0,642
Hombre	56 (276)	20,67 %	20,29 % (15,71-25,52)	ref	
TOTAL	293 (1335)	100 %	21,95 % (19,75-24,27)		
Edad[b]				**1,02 (1,01-1,04)**	**0,006**
Categoría profesional					
Enfermero/a	81 (349)	26,14% (23,80-28,59	23,21 % (18,88-28,00)	1,19 (0,49-2,90)	0,689
TCAE	66 (232)	17,38% (15,38-19,52)	28,45 % (22,74-34,72)	1,70 (0,75-3,87)	0,203
Médico/a	35 (173)	12,96% (11,20-14,89)	20,23 % (14,52-27,00)	0,76 (0,31-1,89)	0,56
Celador/a	30 (132)	9,89% (8,34-11,62)	22,73 % (15,89-30,82)	1,19 (0,49-2,90)	0,71
Personal Técnico	13 (106)	7,94% (6,55-9,52)	12,26 % (6,70-20,06)	0,63 (0,22-1,80)	0,39
Auxiliar administrativo	17 (96)	7,19% (5,86-8,71)	17,71 % (10,67-26,83)	ref	
Personal de servicios	11 (76)	5,69% (4,51-7,07)	14,47 % (7,45-24,52)	1,97 (0,39-10,03)	0,412
MIR	13 (48)	3,60% (2,66-4,74)	27,08 % (15,28-41,85)	1,70 (0,56-5,18)	0,351
Personal de limpieza	9 (36)	2,70% (1,90-3,71)	25,00 % (12,12-42,20)	1,00 (0,27-3,74)	0,999
Otro	17 (83)	6,22% (4,98-7,65)	20,48 % (12,41-30,76)	1,38 (0,54-3,52)	0,507
Desconocido	1 (4)	0,30% (0,08-0,77)	25,00 % (0,63-80,59)		
TOTAL	293 (1.335)	100 %	21,94 % (19,74-24,26)		
Servicio					
Medicina Interna	24 (113)	8,46% (7,03-10,09)	21,24% (14,11-29,94)	1,29 (0,57-2,94)	0,539
Urgencias	26 (110)	8,24% (6,82-9,85)	23,64% (16,06-32,68)	1,50 (0,62-3,63)	0,369
Cirugía general	14 (67)	5,02% (3,91-6,33)	20,90% (11,92-32,57)	ref	
UCI	14 (58)	4,35% (3,32-5,58)	24,14% (13,87-37,17)	1,87 (0,60-5,88)	0,283
Varios	13 (52)	3,90% (2,92-5,08)	25,00% (14,04-38,95)	1,34 (0,49-3,65)	0,567
Radiodiagnóstico	12 (51)	3,82% (2,86-4,99)	23,53% (12,79-37,49)	1,53 (0,49-4,74)	0,464
Consultas externas	11 (48)	3,60% (2,66-4,74)	22,92% (12,03-37,31)	0,82 (0,28-2,41)	0,722
Laboratorio	7 (47)	3,52% (2,60-4,65)	14,89% (6,20-28,31)	1,25 (0,32-4,93)	0,748
Ginecología	11 (46)	3,45% (2,53-4,57)	23,91% (12,59-38,77)	1,26 (0,46-3,51)	0,653
Urología	9 (40)	3,00% (2,15-4,06)	22,50% (10,84-38,45)	0,96 (0,33-2,80)	0,947
Mantenimiento	2 (38)	2,85% (2,02-3,89)	5,26% (0,64-17,75)	0,28 (0,04-2,13)	0,220
Psiquiatría	9 (38)	2,85% (2,02-3,89)	23,68% (11,44-40,24)	1,17 (0,38-3,67)	0,783
Traumatología	6 (36)	2,70% (1,90-3,71)	16,67% (6,37-32,81)	1,01 (0,32-3,14)	0,992
Farmacia	12 (34)	2,55% (1,77-3,54)	35,29% (19,75-53,51)	2,59 (0,80-8,38)	0,112
Cocina	5 (33)	2,47% (1,71-3,45)	15,15% (5,11-31,90)	0,56 (0,10-3,16)	0,509
Nefrología	11 (32)	2,40% (1,65-3,37)	34,38% (18,57-53,19)	1,54 (0,51-4,60)	0,443
Hematología	7 (30)	2,25% (1,52-3,19)	23,33% (9,93-42,28)	1,55 (0,48-4,96)	0,464
Lavandería	4 (30)	2,25% 1,52-3,19)	13,33% (3,76-30,72)	0,50 (0,08-3,28)	0,469
Otros	70 (304)	22,77% (20,55-25,12)	23,03% (18,41-28,17)	1,33 (0,61-2,89)	0,479
Desconocido	24 (100)	7,50% (6,14-9,04)	24,00% (16,02-33,57)		

Tabla 2 **Prevalencia de trabajadores infectados (cont.)**

	Infectados (total)	% de la muestra	% de infectados (IC 95%)	OR[a] (IC 95%)	p
Contacto extralaboral					
No	209 (1.099)	82,32% (80,17-84,33)	19,02% (16,74-21,47)	ref	
Sí	**77 (215)**	**16,11% (14,17-18,19)**	**35,81% (29,41-42,62)**	**2,35 (1,60-3,47)**	**0,000**
Desconocido	7 (21)	1,57% (0,98-2,40)	33,33% (14,59-56,97)		
Factor de riesgo de salud					
Hipercolesterolemia	33 (141)	10,56% (8,96-12,34)	23,40% (16,69-31,27)	1,02 (0,62-1,67)	0,945
HTA	24 (124)	9,29% (7,86-10,97)	19,36% (12,81-27,42)	0,61 (0,34-1,09)	0,093
DM	9 (27)	2,02% (1,34-2,93)	33,33% (16,52-53,96)	1,45 (0,55-3,85)	0,457
EPOC	7 (23)	1,72% (1,10-2,57)	30,44% (13,21-52,92)	1,06 (0,33-3,47)	0,918
Inmunosupresión	6 (19)	1,42% (0,86-2,21)	31,58% (12,58-56,55)	1,14 (0,26-5,11)	0,864
Cardiopatía isquémica	2 (10)	0,75% (0,36-1,37)	20% (2,52-55,61)	0,73 (0,13-4,31)	0,731
Obesidad	4 (8)	0,6% (0,26-1,18)	50% (15,70-84,23)	3,43 (0,60-19,55)	0,164
EPI					
Nunca	25 (100)	7,49% (6,14-9,04))	25% (16,88-34,66)	ref	
A veces	105 (382)	28,61% (26,20-31,12)	27,49% (23,07-32,26)	0,94 (0,51-1,75)	0,848
Siempre	146 (770)	57,68% (54,98-60,35)	18,96% (16,25-21,91)	0,54 (0,29-0,99)	0,047
Desconocido	17 (83)	6,22% (4,98-7,65)	20,48% (12,41-30,76)		
Tareas realizadas					
Anamnesis/exploración	102 (450)	33,70% (31,17-36,32)	22,67% (18,88-26,82)	1,47 (0,92-2,37)	0,111
Nebulizaciones	32 (187)	14,01% (12,19-15,99)	17,11% (12,01-23,29)	**0,46 (0,26-0,82)**	**0,008**
Alto flujo	37 (202)	15,13% (13,25-17,17)	18,32% (13,24-24,35)	0,78 (0,44-1,41)	0,415
Intubación orotraqueal	18 (85)	6,37% (5,12-7,81)	21,18% (13,06-31,39)	1,40 (0,57-3,48)	0,466
Manejo	138 (607)	45,47% (42,77-48,18)	22,74% (19,46-26,28)	0,87 (0,56-1,36)	0,540
Otras	73 (398)	29,81% (27,37-32,35)	18,34% (14,66-22,50)	0,64 (0,37-1,13)	0,122
Horas de trabajo semanales					
<20	5 (18)	1,35% (0,80-2,12)	27,78% (9,70-53,48)	Ref	
21-30	5 (34)	2,55% (1,77-3,54)	14,71% (4,95-31,06)	0,76 (0,13-4,55)	0,761
30-40	170 (810)	60,67% (58-63,31)	20,99% (18,23-23,96)	1,42 (0,35-5,69)	0,623
>40h	104 (439)	32,88% (30,37-35,48)	23,69 (19,79-27,95)	1,21 (0,30-4,92)	0,787
Desconocido	9 (34)	2,55% (1,77-3,54)	26,47% (12,88-44,36)		

[a]OR ajustada mediante regresión logística por el resto de variables incluidas en la tabla

[b]OR por incremento de unidad

En negrita los resultados con p<0,05

El contacto extrahospitalario declarado con un paciente con COVID-19 se asoció a un 16,8% más de prevalencia de infección (IC 95% 10-23,6%, p 0,000).

La síntomas que presentaron una mayor fuerza de asociación con la infección por SARS-CoV-2 fueron anosmia (OR 9,31, IC 95% 4,44-19,55, p 0,000), ageusia (OR 3,05, IC 95%1,37-6,81, p 0,006), y fiebre (OR 5,55, IC 95% 3,40-9,07, p 0,000) (Tabla 3). La tos y la cefalea no presentaron asociación estadística con una mayor prevalencia de infección. El dolor de garganta, y la sensación de mareo tuvieron una asociación significativa con una menor prevalencia de infección.

No apreciamos diferencias estadísticamente significativas en la prevalencia de infección en los diferentes grupos sanguíneos ABO, ni Rh, aunque el grupo AB presentó una tendencia a asociarse a una mayor prevalencia (OR 1,94, IC 95% 0,92-4,08, p 0,083) (Tabla 4).

Tabla 3 Prevalencia de síntomas

Síntoma	Nº de infectados (total)	% de la muestra (IC 95%)	% de infectados (IC 95%)	OR (IC 95%)[a]	p
Fiebre	**137 (209)**	**21,72% (19,54-24,03)**	**65,55% (58,68-71,97)**	**5,55 (3,40-9,07)**	**0,000**
Mialgias	**145 (280)**	**20,97% (18,82-23,26)**	**51,79% (45,76-5,77)**	**1,91 (1,19-3,06)**	**0,007**
Tos	119 (279)	20,90% (18,75-23,18)	42,65% (36,78-48,69)	1,12 (0,69-1,80)	0,650
Dolor de garganta	**84 (244)**	**18,28% (16,24-20,46)**	**34,43% (28,48-40,75)**	**0,59 (0,35-0,99)**	**0,045**
Cefalea	130 (362)	27,12% (24,75-29,59)	35,91% (30,97-41,09)	0,74 (0,47-1,17)	0,200
Anosmia	**135 (165)**	**12,36% (10,64-14,25)**	**81,82% (75,07-87,38)**	**9,31 (4,44-19,55)**	**0,000**
Ageusia	**116 (139)**	**10,41% (8,83-12,18)**	**83,45% (76,21-89,21)**	**3,05 (1,37-6,81)**	**0,006**
Mareo	**42 (94)**	**7,04% (5,73-8,55)**	**44,68% (34,41-55,29)**	**0,42 (0,20-0,89)**	**0,023**
Diarrea	**95 (187)**	**14,01% (12,19-15,99)**	**50,80% (43,41-58,17)**	**1,78 (1,09-2,92)**	**0,021**
Total	293 (1.335)				

[a]**OR ajustada mediante regresión logística según edad y género**

En negrita los resultados con p<0,05

Tabla 4 Prevalencia de infectados en los distintos grupos ABO y Rh

Grupo/Rh	Infectados (total)	% de la muestra	Porcentaje de infectados (IC 95%)	OR (IC 95%)[a]	p
A	101 (421)	31,54% (29,05-34,10)	23,99% (19,99-28,36)	1,27 (0,90-1,79)	0,173
AB	12 (37)	2,77% (1,96-3,80)	32,43% (18,01-49,78)	1,94 (0,92-4,08)	0,083
B	16 (73)	5,47% (4,31-6,83)	21,92% (13,08-33,14)	1,10 (0,60-2,04)	0,754
0	76 (373)	27,94% (25,55-30,43)	20,38% (16,40-24,83)	Ref	
Desconocido	88 (431)	20,42% (16,71-24,54)	20,42% (16,71-24,54)		
Rh (-)	43 (162)	12,14% (10,43-14,01)	26,54% (19,92-34,03)	Ref	
Rh (+)	162 (732)	54,83% (52,12-57,53)	22,13% (19,17-25,32)	0,73 (0,49-1,09)	0,120
Desconocido	88 (441)	19,96% (16,23-24%)	19,96% (16,32-24)		

[a]**OR ajustada mediante regresión logística según edad, género, grupo sanguíneo, y Rh**

Sólo una trabajadora del centro había fallecido por COVID-19 en la primera ola (abril de 2020) [10], antes incluso del inicio de la recogida de datos, lo que sitúa la mortalidad al final de la primera onda epidémica en el 0,06% (IC95% 0,002-0,334%). De los infectados en la primera ola, un 4.43% requirieron ingreso (13) y de éstos, un 38,46% necesitaron de cuidados intensivos (5).

A fecha de septiembre de 2021, según datos proporcionados por el Servicio de Medicina Preventiva de nuestro hospital, no ha habido más muertes entre los TS y TNS del Hospital por COVID-19, siendo el número total de trabajadores infectados 391 (23,45%), y de éstos ingresaron 19 (4,86% de los trabajadores infectados), requiriendo de cuidados intensivos 8 (2%).

DISCUSIÓN

Hemos encontrado una elevada prevalencia de TSyNS infectados por SARS-CoV-2 al final de la primera ola epidémica de la pandemia, similar a la registrada entre la totalidad del personal sanitario en España (RENAVE), y que se sitúa entre las más altas de las publicadas entre trabajadores hospitalarios: 11,2% en personal sanitario en el Hospital Clínico de Barcelona [11], 19,99% en personal sanitario en el Hospital Universitario de Fuenlabrada [9], o el 33,1% en personal sanitario y no sanitario del Hospital Universitario Fundación Alcorcón [12]. Casi la totalidad trabajadores del hospital se contagiaron durante la primera ola de la pandemia (un 2% durante los 17 meses siguientes). Esta elevada prevalencia contrasta con la hallada en el estudio de seroprevalencia en

la población general que el Ministerio de Sanidad y Consumo realizó en aquel momento [8]: 5% en España, 6,9% en Castilla-León, 11,8% en Segovia.

Entre los factores que a juicio de los autores pueden explicar la gran diferencia observada en la prevalencia entre el personal de nuestro hospital y la población a la que atendía, incluso entre aquellos que no prestaron una asistencia directa a pacientes con COVID-19, y la drástica caída en contagios posterior a la primera onda epidémica, creemos que puede estar la mayor exposición a sujetos infectados, sumada a unas medidas de protección insuficientes: carencia inicial de equipos de protección individual en el contexto de una escasez mundial de los mismos, ausencia de circuitos diferenciados para pacientes sospechosos de infección, escasez de pruebas diagnósticas entre trabajadores en un momento de muy baja disponibilidad global, alta prevalencia de trabajadores infectados asintomáticos, y que trabajadores sintomáticos siguieran desempeñando sus funciones ante la escasez de personal.

Se sabe que la edad es un factor de mal pronóstico en la COVID-19, pero hasta donde conocemos ésta es la primera vez que se observa que también es una variable asociada con una mayor prevalencia de la enfermedad.

Se sabe que el uso continuado de las mascarillas autofiltrantes (respiradores), no intermitente, y no sólo en situaciones o tareas identificadas como de riesgo, protegen a los TSyNS del contagio [13]. En concordancia con este hecho hemos observado que uso del EPI se asocia con una menor prevalencia de contagio. Y éste fenómeno podría explicar también la menor prevalencia entre trabajadores que administraron tratamiento nebulizado, un procedimiento que a priori debería tener un efecto contrario por la elevada generación de aerosoles. Creemos que cuando administraba tratamiento nebulizado el trabajador tenía una percepción de mayor riesgo de contagio, y por ello pudo tener mayor diligencia en la utilización de los EPI y/o redujo el tiempo que permaneció en la sala donde se administraban.

La elevada proporción de trabajadores infectados sin síntomas es importante porque contribuyó a la propagación de la infección. No podemos determinar cuántos de los trabajadores infectados asintomáticos lo eran realmente o se encontraban en período pre-sintomático. Sin embargo, los estudios publicados indican que, salvo en personas de edad avanzada, el porcentaje de infectados asintomáticos que desarrollan síntomas más adelante es muy pequeño [14].

La infección por SARS-CoV-2 en TSyNS de nuestro centro hospitalario parece ser un riesgo ocupacional, sin que hayamos encontrado diferencias entre categorías profesionales, servicios, ni duración de la jornada. Incluso los trabajadores que no realizaron atención directa a pacientes con COVID-19 presentan una elevada prevalencia de infección. La edad es una variable asociada a mayor prevalencia de infección. El uso general y continuado del EPI es una medida eficaz para reducir el riesgo de contagio. No hemos encontrado relación entre prevalencia, variables de salud, ni grupo sanguíneo. Fiebre, anosmia, y ageusia, son los síntomas más asociados a la COVID-19.

AGRADECIMIENTOS

Agradecer a todo el personal del hospital que de forma desinteresada participó en el estudio rellenado el cuestionario, así como el interés mostrado por los resultados del estudio.

FINANCIACIÓN

Los autores del estudio declaran no haber recibido financiación alguna para la realización del mismo.

CONFLICTOS DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

BIBLIOGRAFÍA

1. COVID-19 situation update worldwide, as of 8 September 2020. [accessed 8 September 2020]. Available at: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases
2. Instituto de Salud Carlos III. Informes COVID-19. 27 Marzo. 2020 [accessed 23 September 2020]. Available at: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx
3. Instituto Nacional de Estadística. (National Statistics Institute). [accessed 3 January 2021]. Available at:https://www.ine.es/dynt3/inebase/index.htm?padre=517&capsel=517
4. The Diagnostic Kit for IgM / IgG Antibody to Coronavirus (SARS-CoV-2) (Lateral Flow) - New Products - Products & Solutions - Zhuhai Livzon Diagnostics Inc. [accessed 2 August 2020]. Available at: http://www.livzondiagnostics.com/en-us/info/17.html
5. openFDA [accessed 21 September 2020]. Available at: https://open.fda.gov/apis/device/covid19serology/
6. LibreOffice en español - suite ofimática libre, basada en OpenOffice, compatible con Microsoft. [accessed 2 August 2020]. Available at: https://es.libreoffice.org/
7. Epidat: programa para análisis epidemiológico de datos. Versión 4.2, julio 2016. Consellería de Sanidade, Xunta de Galicia, España; Organización Panamericana de la Salud (OPS-OMS); Universidad CES, Colombia. Available at: http://www.sergas.es/Saude-publi.
8. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020;396(10250):535-544. doi: 10.1016/S0140-6736(20)31483-5
9. Barallat J, Fernández-Rivas G, Quirant-Sánchez B, González V, Doladé M, Martinez-Caceres E, et al. Seroprevalence of SARS-CoV-2 IgG specific antibodies among healthcare workers in the Northern Metropolitan Area of Barcelona, Spain, after the first pandemic wave. PLoS One. 2020;15(12):1-10. doi: 10.1371/journal.pone.0244348.

10. Marisol Sacristán, celadora de 57 años, primera víctima mortal del coronavirus en la plantilla del Hospital de Segovia | El Norte de Castilla. [accessed 23 September 2020]. Available at: https://www.elnortedecastilla.es/segovia/marisol-sacristan-anos-20200422233814-nt.html?ref=https:%2F%2Fwww.google.com%2F

11. Garcia-Basteiro AL, Moncunill G, Tortajada M, Vidal M, Guinovart C, Jiménez A, et al. Seroprevalence of antibodies against SARS-CoV-2 among health care workers in a large Spanish reference hospital. Nat Commun. 2020;11(1). doi: 10.1038/s41467-020-17318-x.

12. Galán MI, Velasco M, Casas ML, Goyanes MJ, Rodríguez-Caravaca G Losa-García JE, et al. Hospital-Wide SARS-CoV-2 seroprevalence in health care workers in a Spanish teaching hospital. Enferm Infecc Microbiol Clin. 2020. doi: 10.1016/j.eimc.2020.11.015.

13. MacIntyre CR, Chughtai AA. A rapid systematic review of the efficacy of face masks and respirators against coronaviruses and other respiratory transmissible viruses for the community, healthcare workers and sick patients. Int J Nurs Stud. 2020 ;108:103629. doi: 10.1016/j.ijnurstu.2020.10362

14. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection. Ann Intern Med. 2020;173(5):362-367. doi: 10.7326/M20-3012.

Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/110.2021

Leonardo Lorente[1]
María Lecuona[2]
Alejandra Pérez-Llombet[1]
Adriana González-Mesa[1]
Manuel Callejón[2]
Teresa Delgado Melian[2]
Ines Olaya Garcia[2]
Alejandro Jiménez[3]
María Luisa Mora[1]
Ana Madueño[2]

Sonication did not provide reliability to Maki technique for catheter related bloodstream infection diagnosis

[1]Intensive Care Unit. Hospital Universitario de Canarias. La Laguna, Tenerife, Spain
[2]Microbiology and Infection Control Service. Hospital Universitario de Canarias. La Laguna, Tenerife, Spain
[3]Research Unit. Hospital Universitario de Canarias, La Laguna, Tenerife, Spain

Article history
Received: 3 August 2021; Revision Requested: 22 September 2021; Revision Received: 3 October 2021; Accepted: 26 November 2021; Published: 17 January 2022

ABSTRACT

Objective. The aim of our study was to analyze sonication and Maki techniques for diagnosis of catheter tip colonization and catheter-related bloodstream infection (CRBSI) on patients admitted to ICU.

Material and methods. Observational and prospective study in one Intensive Care Unit. Patients with some central venous catheter (CVC) at least for 7 days and catheter-related infection (CRI) suspicion (new episode of fever or sepsis) were included. We performed Maki technique followed by sonication of catheter tip. We compared area under the curve (AUC) of Maki, sonication, and techniques combination to diagnosis catheter tip colonization and CRBSI.

Results. We included 94 CVC from 87 CRI suspicion episodes. We found 14 cases of catheter tip colonization and 10 cases of CRBSI. Of the 14 catheter tip colonization cases, 7 (50.0%) were detected by Maki and sonication techniques, 6 (42.9%) were detected only by Maki technique, and 1 (7.1%) was detected only by sonication technique. Of the 10 CRBSI, 6 (60.0%) were detected by Maki and sonication techniques, 4 (40.0%) were detected only by Maki technique, and any only by sonication technique. We found higher AUC in Maki technique than in sonication technique to diagnosis of CRBSI (p=0.02) and to diagnosis of catheter tip colonization (p=0.03). No significant differences were found in AUC between Maki technique and combination techniques for diagnosis of catheter tip colonization (p=0.32) and of CRBSI (p=0.32).

Conclusion.: Sonication did not provide reliability to Maki technique for diagnosis of catheter tip colonization and CRBSI.

Keywords: Sonication, Maki, colonization, bloodstream infection

Correspondence:
Leonardo Lorente.
Intensive Care Unit. Hospital Universitario de Canarias. Ofra, s/n. La Laguna - 38320. Tenerife. Spain.
E-mail: lorentemartin@msn.com

La sonicación no proporciona rentabilidad a la técnica de Maki para el diagnóstico de bacteriemia relacionada con catéter

RESUMEN

Objetivo. El objetivo de nuestro estudio fue analizar las técnicas de sonicación y Maki para el diagnóstico de la colonización de la punta del catéter y la bacteriemia relacionada con el catéter (CRBSI) en pacientes ingresados en UCI.

Material y método. Estudio observacional y prospectivo en una Unidad de Cuidados Intensivos. Se incluyeron pacientes con algún catéter venoso central (CVC) insertado al menos durante 7 días y sospecha de sospecha de infección relacionada con el catéter (IRC) (nuevo episodio de fiebre o sepsis). Se realizó técnica de Maki y posteriormente sonicación de la punta del catéter. Comparamos áreas bajo la curva (AUC) de Maki, sonicación y combinación de técnicas para el diagnóstico de colonización de la punta del catéter y de CRBSI.

Resultados. Se incluyeron 94 CVC de 87 episodios de sospecha de IRC. Encontramos 14 casos de colonización de la punta del catéter y 10 casos de CRBSI. De los 14 casos de colonización de la punta del catéter, 7 (50,0%) fueron detectados por Maki y técnicas de sonicación, 6 (42,9%) fueron detectados solo por la técnica de Maki y 1 (7,1%) fue detectado solo por la técnica de sonicación. De los 10 CRBSI, 6 (60,0%) fueron detectados por técnicas de Maki y sonicación, 4 (40,0%) fueron detectados solo por la técnica de Maki, y ninguno solo por la técnica de sonicación. Encontramos mayor AUC con Maki que en la sonicación para el diagnóstico de CRBSI (p=0.02) y para el diagnóstico de colonización de la punta del catéter (p=0.03). No encontramos diferencias significativas en AUC entre Maki technique y combinación de técnicas para el diagnóstico de CRBSI (p=0.32) y para el diagnóstico de colonización de la punta del catéter (p=0.32).

Conclusiones. La sonicación no proporcionó rentabilidad a la técnica de Maki para el diagnóstico de colonización de la punta del catéter y CRBSI.

Palabras clave: Sonicación, Maki, colonización, bacteriemia.

INTRODUCTION

The use of a central venous catheter (CVC) may be needed due to different motives, such as the administration of fluids, blood products, parenteral nutrition, medications, or the monitorization of hemodynamic status. However, the use of those devices has different risks such as catheter related bloodstream infection (CRBSI), which leads to an increase of morbidity, mortality and assistant costs [1-4].

The semiquantitative technique of Maki et al is considered the reference standard to demonstrate catheter tip colonization due to its simplicity [5]. However, a potential disadvantage lies is that as it consists in rolling the catheter tip across the agar then could detect microorganism of external catheter tip surface but could not detect microorganism of internal catheter tip surface. Thus, Maki's technique could give false negative of catheter tip colonization for patients with colonization by an endoluminal mechanism. The possible superiority of quantitative techniques (sonication and vortexing) to catheter tip colonization diagnosis in respect to Maki technique lies of their potential ability to detect catheter tip colonization by exoluminal and also by endoluminal mechanism [6-9]. However, all quantitative methods are time-consuming and due to this its use has not widespread stablished in clinical microbiology laboratories.

There are scarce data about the reliability comparison between Maki's semiquantitative technique and sonication quantitative method for detection of CRBSI [10-13]. Some studies concluded that Maki and sonication methods exhibited similar reliability [10-12] and in one study was found the potential benefit of sonication jointly with Maki method [13].

Recent guidelines for the diagnosis of intravascular catheter- related infection (CRI) recommended that semiquantitative catheter culture by Maki technique and quantitative catheter segment culture by sonication have the same strength of the recommendations and quality of the evidence, which is of A-II [14,15].

Previous studies analyzing sonication and Maki techniques have included CVC from any patient admitted to the hospital and CVC removed due to any motive [10-13]. However, there has been not analyzed sonication and Maki techniques including only CVC from patients admitted to ICU, and CVC removed for catheter-related infection (CRI) suspicion after at least 7 days with that CVC. Therefore, the novel objective of our study was to analyze sonication and Maki techniques including only CVC from patients admitted to ICU, in whom CVC was removed for CRI suspicion, and remained at least 7 days with that CVC.

MATERIAL AND METHODS

Design and subjects. A prospective and observational study was carried out between June 2020 and March 2021 after the approval by the Institutional Ethic Review Board of the Hospital Universitario de Canarias (Tenerife, Spain). The requirement of written informed consent was waived due to the patient visits prohibition by the public health policy of Spanish Government in the COVID-19 pandemia context and due to the only change of our daily clinical practice by the study was the sonication technique (which is a procedure for CRBSI diagnosis that is internationally accepted).

We included patients admitted to ICU and removing CVC for CRI suspicion after at least 7 days with that CVC. CRI suspicion was stablished when a patient developed a new episode of sepsis or fever. We defined sepsis according to Sepsis-3 Consensus criteria of 2016 [16]. We considered fever when temperature was ≥38ºC.

Variables recorded. We recorded the following variables for each patient: Sex, age, admission diagnostic, diabetes mellitus, asthma, chronic liver disease, smoking, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus, hematological tumor, solid tumor. Also, we registered the use of renal replacement therapy, parenteral nutrition, corticosteroids or, immunosuppressive therapy previously to admission. In addition, we recorded the use of corticosteroids, immunosuppressive therapy, parenteral nutrition, propofol or renal replacement therapy at moment of CRI suspicion. Finally, we also registered site of CVC, time of CVC, and death at 30 days.

Sample collections. The following samples were collected from each patient: paired blood samples, catheter-tip and other clinical samples. Paired blood samples were taken from peripheral vein, with 10 ml blood sample in each one and separated by 15 minutes. Catheter-tip sample was taken after scrubbing the skin surrounding the insertion site with 2% chlorhexidine and cutting off the tip (distal 5-cm segment) using sterile scissors. First, we performed catheter-tip culture using the Maki´s technique and then sonication. Maki's semi-quantitative technique was performed by rolling each catheter tip to a blood agar plate [5]. Sonication quantitative technique was performed by placing small fragments of catheter tip in 1 mL of brain-heart infusion broth, then vortexing, sonicating for 1 min (at 35 000 Hz and 125 W), and vortexing for 15 seconds. Finally, 0.1 mL of the sonicated broth was streaked onto sheep blood agar plates [13]. Patients without blood culture, Maki's technique and sonication technique were excluded of the analysis.

Definitions. European Centre for Disease Prevention and Control (ECDC) criteria were used to define infections [17]. We considered catheter-tip colonization as a significant growth of a microorganism on the CVC tip by the semi-quantitative method of Maki et al (≥15 colony-forming units) [5] or by the quantitative method of sonication (≥100 colony-forming units) [13]. CRBSI was defined as a positive blood culture by recognized pathogen, CVC tip colonization with the same microorganism and no other apparent infection source. We defined bloodstream infection of unknown origin (BSIUO) as bloodstream verified during survey and no source found. Primary bloodstream infection (PBSI) includ-

ed CRBSI and BSIUO; therefore, some PBSI had a positive CVC tip colonization (by a semi-quantitative or quantitative method) and others not.

Statistical analysis. We reported categorical variables as frequencies and percentages, and continuous variables as medians and percentiles 25-75. We used chi-square test to compare categorical variables between group, and Mann-Whitney T test to compare continuous variables. Concordance between Maki and sonication techniques for the diagnosis of catheter tip colonization and CRBSI were determined using Cohen´s Kappa test, and the percentages of agreement and disagreement between both techniques were calculated. We carried out receiver operating characteristic (ROC) analyses to diagnosis of catheter tip colonization and of CRBSI by Maki, sonication and combination of both techniques. Comparison of area under the curve (AUC) of ROC curves was carried out using the method of DeLong et al. [18]. We considered a difference as statistically significant when p-values were <0.05. We carried out statistical analysis with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1 **Characteristics of CVC developing or not catheter-related bloodstream infection (CRBSI) and developing or not primary bloodstream infections (PBSI).**

Data	Non CRBSI (n=84)	CRBSI (n=10)	P-value CRBSI vs non	Non PBSI (n=71)	PBSI (n=23)	P-value PBSI vs non
Time of CVC (days); median (p 25-75)	9 (7-12)	10 (9-13)	0.31	9 (7-12)	9 (8-12)	0.75
Site of CVC; n (%)			0.71			0.83
Subclavian	18 (21.4)	3 (30.0)		15 (21.1)	6 (26.1)	
Jugular	45 (53.6)	4 (40.0)		37 (52.1)	12 (52.2)	
Femoral	21 (25.0)	3 (30.0)		19 (26.8)	5 (21.7)	
Age; years (p 25-75)	65 (54-72)	64 (52-71)	0.74	64 (54-72)	64 (52-72)	0.80
Sex female; n (%)	23 (27.4)	0	0.11	20 (28.2)	3 (13.0)	0.17
Admission diagnostic; n (%)			0.38			0.07
Medical	63 (75.0)	9 (90.0)		51 (71.8)	21 (91.3)	
Surgical	14 (16.7)	0		14 (19.7)	0	
Traumatology	7 (8.3)	1 (10.0)		6 (8.5)	2 (8.7)	
Diabetes mellitus; n (%)	23 (27.4)	4 (40.0)	0.47	23 (32.4)	4 (17.4)	0.20
Renal replacement therapy previously to admission ;n (%)	3 (3.6)	1 (10.0)	0.37	2 (2.8)	2 (8.7)	0.25
COPD; n (%)	10 (11.9)	0	0.59	7 (9.9)	3 (13.0)	0.70
Asthma; n (%)	4 (4.8)	1 (10.0)	0.44	3 (4.2)	2 (8.7)	0.59
Chronic liver disease; n (%)	4 (4.8)	0	0.99	4 (5.6)	0	0.57
Smoking; n (%)	14 (16.7)	1 (10.0)	0.99	11 (15.5)	4 (17.4)	0.99
Parenteral nutrition previously to admission; n (%)	1 (1.2)	0	0.99	1 (1.4)	0	0.99
Corticosteroids previously to admission; n (%)	3 (3.6)	0	0.99	3 (4.2)	0	0.99
Immunosuppressive therapy previously to admission; n (%)	4 (4.8)	1 (10.0)	0.44	4 (5.6)	1 (4.3)	0.99
Hematological tumor; n (%)	0	1 (10.0)	0.11	0	1 (4.3)	0.25
Solid tumor; n (%)	1 (1.2)	0	0.99	1 (1.4)	0	0.99
Human Immunodeficiency Virus; n (%)	1 (1.2)	0	0.99	1 (1.4)	0	0.99
Corticosteroids at sepsis; n (%)	12 (14.3)	0	0.35	8 (11.3)	4 (17.4)	0.48
Immunosuppressive therapy at sepsis; n (%)	2 (2.4)	0	0.99	2 (2.8)	0	0.99
Parenteral nutrition at sepsis; n (%)	14 (16.7)	2 (20.0)	0.68	10 (14.1)	6 (26.1)	0.21
Propofol at sepsis; n (%)	34 (40.5)	4 (40.0)	0.99	31 (43.7)	7 (30.4)	0.33
Renal replacement therapy at sepsis; n (%)	7 (8.3)	1 (10.0)	0.99	7 (9.9)	1 (4.3)	0.67
Deaths at 30 days; no. (%)	23 (27.4)	3 (30.0)	0.99	20 (28.2)	6 (26.1)	0.99

CVC = central venous catheter; COPD = Chronic Obstructive Pulmonary Disease

Table 2 Maki and sonication results to detect catheter-tip colonization/catheter-related bloodstream infection.

	Maki +	Maki -	Total
Sonication +	7/6	1/0	8/6
Sonication -	6/4	80/84	86/88
Total	13/10	81/84	94/94

RESULTS

We included 94 CVC from 87 patients with CRI suspicion. We found 23 PBSI, 10 (43.5%) were CRBSI and 13 (56.5%) were BSIUO. We no found significant differences between group of CVC developing CRBSI (n=10) and no developing it (n=84) in rate of death (p=0.99), time of CVC, site of CVC, and in other variables (Table 1). Neither we found significant differences between group of CVC developing PBSI (n=23) and no developing it (n=71) in rate of death (p=0.99), time of CVC, site of CVC, and in other variables (Table 1).

We found 14 cases of catheter tip colonization of which 10 were cases of CRBSI. Of the 14 catheter tip colonization cases, 7 (50.0%) were detected by Maki and sonication techniques, 6 (42.9%) were detected only by Maki technique, and 1 (7.1%) was detected only by sonication technique (Table 2). Of the 10 CRBSI, 6 (60.0%) were detected by Maki and sonication techniques, 4 (40.0%) were detected only by Maki technique, and any only by sonication technique (Table 2).

The AUC to diagnosis of CRBSI was for Maki technique of 98% (95% CI = 93%-99%; p<0.001), by sonication technique of 79% (95% CI = 69%-87%; p<0.001) and by techniques combination of 98% (95% CI = 92%-99%; p<0.001). We found higher AUC in techniques combination than in sonication technique (p=0.02) and in Maki technique than in sonication technique (p=0.02) to diagnosis of CRBSI. No significant differences were found in AUC between Maki technique and combination techniques (p=0.32).

The AUC to diagnosis of catheter tip colonization was for Maki technique of 96% (95% CI = 90%-99%; p<0.001), by sonication technique of 79% (95% CI = 69%-86%; p<0.001) and by techniques combination of 100% (95% CI = 96%-100%; p<0.001). We found higher AUC in techniques combination than in sonication technique (p=0.002) and in Maki technique than in sonication technique (p=0.03) to diagnosis of catheter tip colonization. No significant differences were found in AUC between Maki technique and combination techniques (p=0.32).

The agreement between Maki and sonication techniques for catheter tip colonization was 92.6%, and Maki technique showed 1/94 (1.1%) false negatives (Cohen´s Kappa: 0.63 (95% CI: 0.38-0.88); P< 0.001) The agreement between Maki and sonication techniques for CRBSI was 95.7%, and Maki technique showed 0/94 false negatives (Cohen´s Kappa: 0.73 (95% CI: 0.48-0.98); P< 0.001).

We found that *Staphylococcus epidermidis* was the most frequent microorganism responsible of catheter tip colonization (Table 3) and CRBSI (Table 3).

DISCUSSION

Previous studies analyzing Maki and sonication method for the diagnosis of catheter tip colonization have included CVC from any patients admitted to the hospital and CVC removed due to any motive [10-13]. Some of those studies concluded that Maki and sonication methods exhibited similar reliability [10-12] and in one study was found the potential benefit of sonication jointly with Maki method [13]. In the study by Guembe et al [13] were included 252 CVCs and the authors found a colonization rate of 14.3% (36/252) and a CRBSI rate of 5.9% (15/252). Of the 36 CVC colonizations, 21 (58.3%) were detected by Maki and sonication, 6 (16.7%) only by Maki technique, and 9 (25.0%) only by sonication technique. Of 15 CRBSI, 11 cases (73.3%) were detected by Maki and sonication, and 4 cases (26.7%) only by sonication technique [13]. The authors concluded that both techniques are complementary and they recommended sonicating fragments

Table 3 Microorganism responsible of catheter tip colonization/catheter-related bloodstream infection obtained by Maki/or and sonication techniques.

Microorganism	Total	Both techniques positives	Maki positive only	Sonication positive only
Staphylococcus epidermidis	8/5	1/1	6/4	1/0
Enterococcus faecalis	1/1	1/1	0/0	0/0
Escherichia coli	1/1	1/1	0/0	0/0
Klebsiella spp.	2/2	2/2	0/0	0/0
Enterobacter cloacae	1/1	1/1	0/0	0/0
Pseudomonas aeruginosa	1/0	1/0	0/0	0/0
TOTAL	14/10	7/6	6/4	1/0

of patients with bacteremia of unknown origin and a negative catheter tip culture by the Maki technique [13].

We only found one catheter tip colonization by sonication that was not detected by Maki technique, and this colonization was not responsible of CRBSI. We found higher AUC in Maki technique than in sonication technique for diagnosis of catheter tip colonization and of CRBSI, and no significant differences were found in AUC between Maki technique and combination techniques for diagnosis of catheter tip colonization and of CRBSI. Thus, in our study, the use of sonication no added any rentability in the diagnosis of CRBSI by Maki technique.

The different results obtained between Gembe et al [13] and our study would be explained because in that study, CVC were collected from a general population (which included ICU and non-ICU adult patients) and CVC had different catheter duration (short and long-term). However, in our study CVC were collected from ICU adult patients and were mainly short term (which have mainly an extraluminal colonization). As sonication is more reliable to detect intraluminal colonization (which appears over all in long-term catheters), it may have no impact at all in the present study, which only included CVC from ICU adult patients, that were mainly short term, which most would be most detected by Maki technique.

Recent guidelines for CRI diagnosis recommended that semiquantitative catheter culture by Maki technique and quantitative catheter segment culture by sonication have the same strength of the recommendations and quality of the evidence [4,15]. We think that the greater simplicity of Maki's semiquantitative technique, the results of our study and the results of other studies makes Maki procedure as the technique of choice for routine work in the microbiology laboratory, and that the use of sonication technique did not provide profitability to the Maki technique for the diagnosis of CRBSI. Skin-colonizing microorganisms (as coagulase-negative staphylococci) are more likely to colonize the external surface of catheter and are the most isolated microorganism in the series, and this fact would explain the absence of profitability of sonication in ICU patients.

Some limitations must be recognized in our study. First, we have not taken other quantitative techniques (as vortexing) to compare its profitability for CRBSI diagnosis with Maki technique and sonication. Second, we have not reported what proportion of CVC were excluded due to have not all culture (blood, Maki technique and sonication technique). Third, sonication was performed after Maki technique in all catheter tip; thus, Maki technique could cause a great loose of microbial load (as bacteria were already discharged by Maki) and sonication would be in disadvantage. Fourth, the sample size of our study could be relatively low; however, it was enough to find that higher AUC in techniques combination than in sonication technique and in Maki technique than in sonication technique for diagnosis of catheter tip colonization and of CRBSI. The sample size to find higher significant AUC in techniques combination than in Maki technique was of 220 CVC for diagnosis of catheter tip colonization and of 5,235 CVC for diagnosis CRBSI.

The novel aspect of our study was that we analyzed sonication and Maki techniques including only CVC from patients admitted to ICU, in whom CVC was removed for CRI suspicion, and remained at least 7 days with that CVC. In our study, sonication did not provide reliability to Maki´s technique for CRBSI diagnosis.

FUNDING

This study was supported by a grant from Fundación DISA a la Investigación Médica 2019 (Santa Cruz de Tenerife. Spain) and a grant from Instituto de Salud Carlos III (PI-18-00500) (Madrid, Spain) and co-financed with Fondo Europeo de Desarrollo Regional (FEDER).

CONFICTS OF INTEREST

All the authors state that they have no conflicts of interest

REFERENCES

1. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994;271(20):1598-601. doi: 10.1001/jama.271.20.1598.
2. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect. 2006;63(2):124-32. doi: 10.1016/j.jhin.2005.12.016.
3. Siempos II, Kopterides P, Tsangaris I, Dimopoulou I, Armaganidis AE. Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta-analysis. Crit Care Med. 2009;37(7):2283-9. doi: 10.1097/CCM.0b013e3181a02a67.
4. Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis. 2011;11(1):30-8. doi: 10.1016/S1473-3099(10)70258-9.
5. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous catheter-related infection. N Engl J Med.1977; 296(23):1305-9. doi: 10.1056/NEJM197706092962301.
6. Cleri DJ, CorradoML, SeligmanSJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis. 1980 Jun;141(6):781-6. doi: 10.1093/infdis/141.6.781.
7. Linares J, Sitges-Serra A, Garau J, Perez L, Martin R. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. J Clin Microbiol. 1985;21(3):357-60. doi: 10.1128/jcm.21.3.357-360.1985.
8. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter–related sepsis: critical level of quantitative tip cultures. Arch Intern Med. 1987;147(5):873-7. PMID: 3555377
9. Sherertz RJ, Raad II, Belani A, Koo LC, Rand KH, Pickett DL. Three-

year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol. 1990; 28(1):76-82. doi: 10.1128/jcm.28.1.76-82.1990.

10. Bouza E, Alvarado N, Alcalá L, Sánchez-Conde M, Pérez MJ, Muñoz P, et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis. 2005;40(8):1096-100. doi: 10.1086/428576.
11. Slobbe L, El Barzouhi A, Boersma E, Rijnders BJ. Comparison of the roll plate method to the sonication method to diagnose catheter colonization and bacteremia in patients with long-term tunnelled catheters: a randomized prospective study. J Clin Microbiol. 2009;47(4):885-8. doi: 10.1128/JCM.00998-08.
12. Erb S, Frei R, Schregenberger K, Dangel M, Nogarth D, Widmer AF. Sonication for diagnosis of catheter-related infection is not better than traditional roll-plate culture: a prospective cohort study with 975 central venous catheters. Clin Infect Dis. 2014;59(4):541-4. doi: 10.1093/cid/ciu352.
13. Guembe M, Martín-Rabadán P, Cruces R, Pérez Granda MJ, Bouza E. Sonicating multi-lumen sliced catheter tips after the roll-plate technique improves the detection of catheter colonization in adults. J Microbiol Methods. 2016; 122:20-2. doi: 10.1016/j.mimet.2016.01.004.
14. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Diagnosis and treatment of catheter-related bloodstream infection: Clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC). Med Intensiva. 2018;42(1):5-36. doi: 10.1016/j.medin.2017.09.012.
15. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Executive summary: Diagnosis and Treatment of Catheter-Related Bloodstream Infection: Clinical Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC). Enferm Infecc Microbiol Clin (Engl Ed). 2018;36(2):112-119. doi: 10.1016/j.eimc.2017.10.019.
16. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10. doi: 10.1001/jama.2016.0287.
17. European Centre for Disease Prevention and Control. Point prevalence survey of health care associated infections and antimicrobial use in European acute care hospitals–protocol version 4.3. Stockholm: ECDC; 2012. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0512-TED-PPS-HAI-antimicrobial-use-protocol.pdf
18. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44:837-45. PMID: 3203132.

Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/128.2021

Methicillin-resistant *Staphylococcus epidermidis* infectious keratitis: Clinical and microbiological profile

Lourdes Vidal Oliver[1]
Patricia Bayo Calduch[1]
Lorena Forqué Rodríguez[2]
David Navarro Ortega[2,3]
Antonio Miguel Duch Samper[1,3]
Javier Colomina Rodríguez[2]

[1]Opthalmology department, Hospital Clínico Universitario, Valencia.
[2]Microbiology department, Hospital Clínico Universitario, Valencia.
[3]Facultat de Medicina, Universitat de València.

Article history
Received: 7 September 2021; Revision Requested: 12 October 2021; Revision Received: 2 November 2021; Accepted: 26 November 2021; Published: 24 January 2022

ABSTRACT

Introduction. *Staphylococcus epidermidis* (SE) is a common cause of bacterial keratitis in certain geographic areas. A high percentage of resistance to methicillin is shown, which gives it cross resistance to beta-lactams and sometimes resistance to other antibacterial groups. We analyzed clinical and microbiological variables in patients with infectious keratitis due to SE.

Methods. Medical records of 43 patients with suspected infectious keratitis and microbiological confirmation for SE, between October 2017 and October 2020, were retrospectively studied. Clinical characteristics (risk factors, size of lesions, treatment, evolution) and microbiological (susceptibility to antibiotics) were analyzed, and groups of patients with methicillin-resistant (MRSE) and methicillin-susceptible (MSSE) infection were compared.

Results. MRSE was present in 37.2% of infectious keratitis. All isolates were sensitive to vancomycin and linezolid. Rates of resistance to tetracyclines and ciprofloxacin were 50% and 56% in the MRSE group, and 11% and 7% in the MSSE group. The clinical characteristics, including size of lesion, visual axis involvement, inflammation of anterior chamber, presence of risk factors and follow-up time, did not show statistically significant differences between groups.

Conclusions. MRSE is a common cause of infectious keratitis caused by SE and shows a high rate of multidrug resistance. Clinically, it does not differ from MSSE keratitis. Additional work is needed to confirm these findings.

Keywords: keratitis, *Staphylococcus epidermidis*, methicillin-resistant.

Correspondence:
Javier Colomina Rodriguez.
Servicio de Microbiología, Hospital Clínico Universitario de Valencia.
E-mail: jcolominarodri@yahoo.es

Queratitis infecciosa por *Staphylococcus epidermidis* resistente a meticilina: perfil clínico y microbiológico

RESUMEN

Introducción. *Staphylococcus epidermidis* (SE) es una causa frecuente de queratitis bacteriana en ciertas áreas geográficas. Presenta un alto porcentaje de resistencia a meticilina, lo que confiere resistencia cruzada a beta-lactámicos y en algunas ocasiones también resistencia a otros grupos de antibacterianos. Analizamos variables clínicas y microbiológicas en pacientes con queratitis infecciosa por SE.

Métodos. Se analizaron retrospectivamente las historias clínicas de 43 pacientes con sospecha de queratitis infecciosa y confirmación microbiológica para SE, entre octubre de 2017 y octubre de 2020. Se analizaron las características clínicas (factores de riesgo, tamaño de las lesiones, tratamiento, evolución) y microbiológicas (susceptibilidad a antibióticos) y se compararon grupos de pacientes con infección resistente (MRSE) y sensible a meticilina (MSSE).

Resultados. El 37,2% de las queratitis fueron por MRSE. Todos los aislados fueron sensibles a vancomicina y linezolid. Las tasas de resistencia a tetraciclinas y ciprofloxacino fueron 50% y 56% en el grupo de MRSE, y 11% y 7% en el grupo de MSSE. Las características clínicas, incluido el tamaño de la lesión, la afectación del eje visual, la inflamación de la cámara anterior, la presencia de factores de riesgo y el tiempo de seguimiento, no mostraron diferencias estadísticamente significativas entre los grupos.

Conclusiones. MRSE es una causa frecuente de las queratitis infecciosas producidas por SE y presenta una alta tasa de resistencia a múltiples fármacos. Clínicamente, no muestra diferencias clínicas con la queratitis por MSSE. Se necesitan trabajos adicionales para confirmar estos hallazgos.

Palabras clave: queratitis, *Staphylococcus epidermidis*, resistente a meticilina.

INTRODUCTION

Gram-positive bacteria are the most common culture-isolated microorganisms in bacterial keratitis according to several series [1-4]. Methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis has been widely described [5-8]. However, literature related to methicillin-resistant *Staphylococcus epidermidis* (MRSE) is limited. Goodman et al. first reported two cases of MRSE keratitis in 1988 [9]. The prevalence has increased since then as showed in larger epidemiological studies, ranging from 34 to 79% [2,3,10].

S. epidermidis is opportunistic bacteria found in the normal skin microbiota and frequently acquires resistance to antibiotics [11-13]. MRSE is resistant to beta-lactams and frequently acquires resistance to other antibiotics for ophthalmological use such as quinolones or tetracyclines. At sites with poor immunosurveillance, such as foreign bodies, MRSE can cause infections and develop biofilms, making it difficult for antibiotics to interact with bacteria, increasing their resistance and making treatment more difficult [14]. The intact cornea and tear layer create a physical immune barrier that prevents opportunistic microorganisms, with limited pathogenicity, from causing infections, which is critical due to the almost complete absence of leukocytes in the tear fluid and corneal layer [15,16]. However, damage to this barrier facilitates microorganisms penetration and, consequently, infection.

We present the clinical characteristics, antibiotic resistance, and treatment results of patients with culture-confirmed MRSE keratitis compared to those with methicillin-sensitive *S. epidermidis* keratitis (MSSE) who attended the Ophthalmology Service in a period of three years.

METHODS

Corneal scrape samples were reviewed retrospectively at the Microbiology Service of the Hospital Clínico Universitario of Valencia during the period between October-2017 and October-2020.

All cases were diagnosed on the first visit as suspected infectious keratitis after slit lamp examination. The criteria considered were conventional: corneal lesion with stromal infiltration (with or without cells in the anterior chamber), pain, discomfort and redness, together with the patient's anamnesis including previous ocular risk factors [1]. To avoid including colonization samples in our study, we included only symptomatic patients with inflammation signs in slit lamp examination.

Patients with monomicrobial culture for *S. epidermidis* and compatible clinical manifestations were included. The clinical history, microbiological results and available slit lamp photographs of all patients were reviewed. Clinical information collected included: patient's age and sex, ocular risk factors, number of follow-up days required, size of the lesion at the time of diagnosis, visual axis involvement and clinical outcomes. All patients were managed in the outpatient clinic.

Patients were divided into severe and non-severe infectious keratitis, according to the following criteria: cells in the anterior chamber, size of the lesion>3 mm and/or involvement of the visual axis.

The size, maximum and minimum, of the infiltrate in millimeters was measured using the ruler adjusted to the slit lamp, as well as photographic control.

Sample collection and microbiological study. All samples were collected in the ophthalmology unit by corneal scraping procedure, direct inoculation onto appropriate culture media [3] and rapid shipment (within 2 hours) to the microbiology laboratory. Blood and chocolate agar plates were incubated in 10% carbon dioxide environments at 35°C for 5-7 days. To exclude accidental contaminants, the criterion to consider a positive culture was the monomicrobial growth of at least 10 colonies on a solid medium with similar morphology to the Gram stain. Cultures that isolated multiple organisms were excluded. Bacterial identification was carried out using MALDI-TOF technology (Bruker Daltonics). Antibiotic susceptibility studies were performed by broth microdilution (MicroScan, Beckman) and the minimum inhibitory concentrations (MIC) obtained were interpreted according to EUCAST guidelines. Antibiotics analyzed in all isolated bacterial strains were: cloxacillin, cotrimoxazole, erythromycin, clindamycin, ciprofloxacin, vancomycin, linezolid, daptomycin, tetracycline, rifampin, fusidic acid, mupirocin, chloramphenicol, and gentamicin.

Treatment and follow-up. After diagnosis, patients were empirically treated hourly, according to American Academy of Ophthalmology, with fortified eye drops of ceftazidime (50mg/ml) and vancomycin (50mg/ml), or ceftazidime (50mg/ml) and tobramycin (50mg/ml), or with fluoroquinolones (3-5mg/ml), along with cyclopentolate 10 mg/ml every 8 hours; the final treatment decision was made according to physician's discretion.

The first check-up was carried out 48 hours after the diagnosis in all cases, and at this time the evolution was classified as either good or suboptimal. The patients were followed-up and days until resolution of lesion (absence of fluorescein corneal lesion's staining and absence of inflammation signs) were counted.

Statistical analysis. All the statistical analyses were performed using SPSS, Version 27, computer software (IBM, Armonk, NY, USA). Binary variables were analysed using chi-square or Fisher's exact test (when expected value <5). Quantitative variables were analyzed with t-test when assuming normal distribution of the data and U-Mann-Whitney when it was not.

A p-value <0.05 was considered statistically significant. Antibiotic resistance was calculated in percentages.

RESULTS

During the study period, forty-three patients with clinical

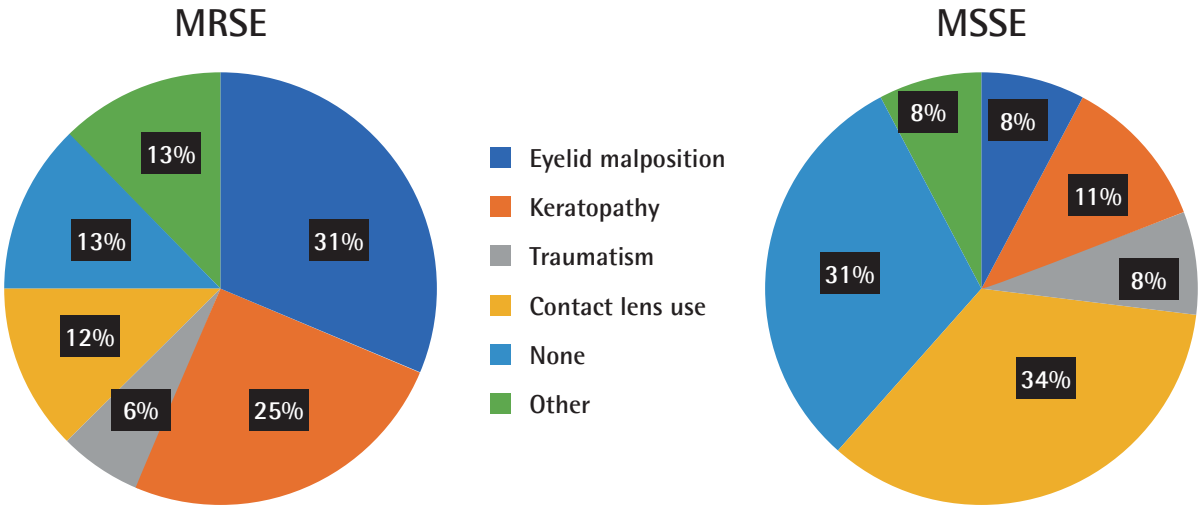


Figure 1 | **Risk factors of MRSE and MSSE keratitis cases.**

MRSE: methicillin-resistant *Staphylococcus epidermidis*, MSSE: methicillin-susceptible *Staphylococcus epidermidis*.

diagnosis of keratitis showed a monomicrobial culture for *S. epidermidis*, 16 of which were resistant to methicillin (37.2%).

Four patients were excluded due to probable contamination: three cases had clinically small marginal infiltrates associated with an epithelial defect and were mildly symptomatic, and the other case had a spongy margin ulcer and torpid evolution, in which subsequent cultures were positive for *Aspergillus*.

Patient characteristics. Patient's mean age was 55.1 years, ranging from 11 to 89 years (MRSE group: 62.6 years, range 23-82 years; MSSE group: 50.7 years, range 11-89 years; p = 0.094). Twenty-two patients were women (51.2%), with no statistical differences between the two *S. epidermidis* groups.

Clinical characteristics. All cases presented with pain and redness of the affected eye, along with one or more epithelial defects and perilesional stromal infiltration.

The mean size of the lesion in maximum and minimum diameter was 1.68x1.05mm (MRSE group: 2.1x1.17mm; MSSE group 1.44x0.97mm; p=0.102 for maximum diameter and p=0.812 for minimum diameter).

Twenty-one patients (48,8%) presented with inflammation in the anterior chamber (MRSE group: n=10, 62.5%; MSSE group: n=11, 40.1%; p=0.083). Five patients had dense stromal edema, making the assessment of the anterior chamber impossible with slit lamp examination. Twenty-nine patients (67.4%) were classified after with criteria of severe keratitis (MRSE group: n=13, 81.3%; MSSE group: n=16, 59.3%; p=0.186). The lesion affected the visual axis in 15 cases (MRSE group: n=6, 37.5%; MSSE group: n=9, 33.3%; p=0.782).

All cases were unilateral, suggesting local risk factors rather than systemic conditions.

The mean follow-up time was 18,5 days until the cessation of the disease (MRSE group: 27.4 days, range 2-166 days; MSSE group: 13 days, range 2-59 days; p=0.129).

The medical records review did not show previous antibiotic treatment or hospital care in the last 4 weeks.

Risk factors and clinical outcomes. Ocular or systemic predisposing factors were present in 33 cases (76.7%). The risk factors include: eyelid malposition, keratopathy, traumatism, contact lens use, none and other (including antiglaucomatous topical medication, intellectual disability, systemic immunosuppression and chronic lacrimal obstruction). The MRSE keratitis are most commonly associated with eyelid malposition (31%) and previous keratopathy (25%) (Figure 1). The MSSE keratitis' main risk factors are contact lens use (34%) and keratopathy (11%). Only 13% of cases in the MRSE group occurs without predisposing conditions, whereas 31% in the MSSE group.

MRSE group (n= 16). Fourteen cases of 16 (87.5%) occurred in eyes with previous risk factors or systemic predisposing conditions such as: lagophthalmos (3), contact lens use (2), neurotrophic keratopathy (2), distichiasis (2), traumatism (1), bullous keratopathy (1), penetrant keratoplasty (1), intellectual disability (1) and chronic use of antiglaucomatous topical medication (1). In 2 cases no prior risk factors were identified.

The outcomes were: corneal thinning (2), central leucoma affecting visual axis (2), penetrant keratoplasty (1) and total corneal opacity (1). The other 10 cases resolved without functional sequelae. The clinical and epidemiological characteristics are shown in Table 1.

MSSE group (n= 27). Eight of the 27 cases (29,6%) did not present ocular risk factors or systemic conditions. The risk

Table 1 Cases of keratitis in the MRSE group and clinical characteristics.

Patient	Sex	Age (years)	Risk factor	Follow-up (days)	Size (max. x min. size) (mm)	Visual axis
1	Female	82	Lagophthalmos	15	3.5x1.2	No
2	Female	75	Bullous keratopathy	8	4.5x4	Yes
3	Female	49	Penetrant keratoplasty	18	2x1	No
4	Male	82	Lagophthalmos	36	2x1	Yes
5	Male	60	Traumatism	2	0.4x0.2	No
6	Male	47	Lagophthalmos	166	0.9x0.8	Yes
7	Female	65	Neurotrophic keratopathy	59	1x0.8	Yes
8	Female	82	Distichiasis	26	Not available	Yes
9	Female	37	Contact lens use	9	0.2x0.2	No
10	Female	59	None	10	1.7x1	No
11	Female	66	Neurotrophic keratopathy	29	5.8x3.5	Yes
12	Female	41	Intellectual disability	8	1.7x0.2	No
13	Male	76	None	20	4x0.2	No
14	Female	80	Antiglaucomatous topical medication	13	1.3x1	No
15	Female	77	Distichiasis	8	1x1	No
16	Female	23	Contact lens use	11	1.5x1.5	No

MRSE: methicillin-resistant *Staphylococcus epidermidis*.

factors present in the other 19 patients were: contact lens use (10), traumatism (2), neurotrophic keratopathy (2), bullous keratopathy (1), distichiasis (1), systemic immunosuppression (1), chronic lacrimal obstruction (1) and floppy eyelid syndrome (1).

The outcomes were: mild leucoma without visual impairment in 23 cases, total corneal opacity (2), endophthalmitis (1) and corneal thinning (1).

A p=0.337 was calculated comparing the presence of any risk factor between MRSE and MSSE group.

Treatment and bacterial sensitivity to antibiotics. Of all cases with severe keratitis criteria (29), 20 (69%) were empirically treated with fortified eye drops of antibiotics administered hourly for 48 hours: 9 cases were treated with ceftazidime and tobramycin and 11 cases with ceftazidime and vancomycin. The other 9 (31%) cases were empirically treated with commercial antibiotics: 2 with topical moxifloxacin (5mg/ml) and 7 with ciprofloxacin (3mg/ml). At the 48-hour check-up, if the clinical evolution was suboptimal, the treatment was adjusted according to the antibiogram.

The initial regime with commercial topical quinolones was maintained in all 9 (100%) cases due to good clinical evolution (less corneal infiltrate, less symptoms and/or decreased inflammation in the anterior chamber).

Of the 9 cases initially treated with ceftazidime and tobramycin, in 3 (33%) cases the same antibiotics were maintained due to good clinical evolution and rapid clinical resolution. The remaining 6 (66%) were changed after receiving antibiogram results: 2 to fortified vancomycin and one to amikacin, whereas the other 3 were shifted to commercial ciprofloxacin.

Out of the 11 cases treated initially with fortified ceftazidime and vancomycin, 2 (18%) patients were kept with the same treatment due to rapid resolution of the infection in one case and because of suboptimal response in the other case. The rest (9, 82%) were adjusted after antibiogram results. 1 was changed to fortified vancomycin after showing resistance to the other antibiotics commercially available, and the rest (8) were switched to commercial medication: one to gentamycin (3mg/ml), 3 to ciprofloxacin (3mg/ml), 3 to moxifloxacin (5mg/ml) and 1 to tobramycin (3mg/ml).

Of the cases that did not meet criteria for severe keratitis (14), 10 (71%) were treated initially with topical ciprofloxacin hourly for 48 hours; this regime was maintained after the complete resolution of the infiltrate, with good clinical evolution and no side effects in all cases. Two (14%) cases were treated initially with ceftazidime and tobramycin (both with good clinical evolution), and 2 (14%) with ceftazidime and vancomycin (one of them with suboptimal evolution).

Comparative results of antibiotic susceptibility are shown in the Table 2. In the MRSE group, there were significant rates of resistance to ciprofloxacin (56%), tetracycline (50%), fusidic acid (45%) mupirocin (73%), and erythromycin (100%). Changes in MIC_{90} of the following antibiotics were detected:

Table 2 Percentages of antibiotics resistance in MRSE and MSSE groups.

	MRSE (N=16)		MSSE (N=27)		
	% Resistance	MIC_{90}	% Resistance	MIC90	p
Cloxacillin	100	>2	0	≤0.25	<0.001*
Cotrimoxazole	13	≤2/38	7	≤2/38	0.578
Erythromycin	100	>4	74	>4	0.026*
Clindamycin	75	0.5	33	0.5	0.063
Ciprofloxacin	56	>2	7	≤1	<0.001*
Vancomycin	0	4	0	2	
Linezolid	0	4	0	2	
Daptomycin	0	≤1	0	≤1	
Tetracycline	50	>8	11	2	0.005*
Rifampicin	0	≤0.5	0	≤0.5	
Fusidico	45	>2	8	≤2	0.013*
Mupirocin	73	>256	24	<256	0.02*
Chloramphenicol	0	≤8	0	≤8	
Gentamicin	38	>8	18	4	0.168
Tobramycin	44	>8	30	8	0.348

MRSE: methicillin-resistant *Staphylococcus epidermidis*, MSSE: methicillin-susceptible *Staphylococcus epidermidis*. MIC_{90} value was defined as the lowest concentration of the antibiotic at which 90% of the isolates were inhibited. *P<0.05

linezolid, vancomycin, ciprofloxacin, tetracycline, fusidic acid, mupirocin and aminoglycosides. In vitro, the best results were obtained with linezolid, vancomycin, daptomycin, chloramphenicol and rifampicin.

Treatment outcomes in MSSE and MRSE groups. Cases of severe and non-severe keratitis in MRSE and MSSE groups with good clinical response after empirical treatment are showed in Table 3. At 48-hour follow-ups, 20 (74%) cases of MSSE keratitis presented with good clinical evolution, and 13 (81%) cases in the MRSE group (p= 0,719).

Of those with suboptimal clinical response (10/43; 23%), the initial treatment was: quinolones (1, 1%; in MSSE group); ceftazidime and tobramycin (3, 30%; 2 MRSE group and 1 MSSE group) and ceftazidime and vancomycin (6, 60%; 1 MRSE group and 5 MSSE group).

Of all the 19 cases of keratitis treated initially with commercial ciprofloxacin, 18 (95%) cases showed a good clinical evolution after 48 hours. The only patient with suboptimal response was classified as severe keratitis in the MSSE group (n=1; 5%).

In severe keratitis caused by MRSE, the ceftazidime and vancomycin regime showed an 80% efficacy (4 out of 5), and a 60% efficacy (3 out of 5) with ceftazidime and tobramycin combination treatment, p>0,99. In MSSE group, treatment with ceftazidime and tobramycin showed outcomes of 33% and 75% respectively in severe keratitis and 50% and 100% in non-severe, p>0,99

DISCUSSION

According to recommendations from the American Academy of Ophthalmology, bacterial keratitis are commonly treated with ciprofloxacin as empirical treatment [17]. However, MRSE is associated with in vitro resistance to this antibiotic, as well as to others commonly used in the ophthalmic clinical practice such as tobramycin [12,18].

Some (75%) of the infections presented in this study resolved after antibiotic treatment with fortified topical antibiotics. The rest were treated with commercial ciprofloxacin, also with good clinical response including severe cases. We found no differences among the different treatment regimes in both groups. Therefore, the evolution of the infection not only depends on treatment, but other aspects such as patient's risk factors or initial presentation of the lesion must also be taken into account.

In case of progression to endophthalmitis, oral linezolid may be a valid choice, since it has shown excellent antibacte-

Table 3 **Cases of severe and non-severe keratitis in MRSE and MSSE groups with good clinical response after 48 hours of empirical treatment.**

	Severe (N=29)		Non-severe (N=14)		
	MRSE (N=13)	MSSE (N=16)	MRSE (N=3)	MSSE (N=11)	% total
Fluoroquinolones	3 (100%)	5 (83%)	3 (100%)	7 (100%)	18 (95%)
Ceftazidime + vancomycin	4 (80%)	2 (33%)	0 (0%)	1 (50%)	7 (54%)
Ceftazidime + tobramycin	3 (60%)	3 (75%)	0 (0%)	2 (100%)	8 (73%)

MRSE: methicillin-resistant *Staphylococcus epidermidis*, MSSE: methicillin-susceptible *Staphylococcus epidermidis*.

rial sensitivity and has a good intraocular penetration that has been previously reported [19].

In the infectious pathology of the anterior pole of eye, ocular microbiota are the most frequently documented causing infection, showing that the border between commensal microbiota and pathogenic microorganism is increasingly thin. Previous studies highlight the colonization rate of *Staphylococcus* species on the ocular surface of healthy eyes, with *S. epidermidis* being the most frequently isolated microorganism [11, 12, 20]. The patient's medical history and a careful slit lamp ophthalmologic evaluation are important to rule out possible false positives from microbiological analysis.

These multidrug resistant bacteria are not rare findings in the clinical practice. In this study, a rate of 37.2% of MRSE is presented, which is similar to other publications [2,3]. Our study supports the hypothesis that the loss of ocular surface homeostasis can lead to corneal ulcers and stromal infiltration, since the majority of cases were associated with risk factors.

In our experience, MRSE infections have shown to be clinically similar to those caused by MSSE, as all the parameters analyzed showed no statistical significance (follow-up time, presence of risk factors, size of the lesion, anterior chamber inflammation or clinical response at 48h check-up). However, MRSE have shown to have higher in vitro resistances to common antibiotics.

Recent reports document multi-site infections with extremely resistant *S. epidermidis* to antibiotics, including linezolid, vancomycin, and teicoplanin [21,22]. This represents a major health problem in the near future, not only related to ophthalmological conditions but also to systemic infections that could lead to the death of a patient.

We consider the relevance of the microbiological analysis in all keratitis, not only in severe cases, in order to establish the etiology and to adequately treat patients with specific medication, so as not to contribute to increase antibiotic resistance in the future.

The main limitation of study is the small number of patients included, although to our knowledge there are no long comparative series of *S. epidermidis* keratitis. Other limitations are its retrospective design and the inherent differences in clinical and therapeutic actions during patient management. In order to minimize the risk of overdiagnosis and attribute the etiology to the local eye microbiota, samples from the healthy eye and the affected eye could have been analyzed in parallel, in order to confirm the findings of the cultures.

MRSE is a frequent cause of keratitis at our institution, especially in patients with ocular risk factors (eyelid abnormalities, previous keratopathy, traumatism or contact lens use). In our cohort, keratitis caused by MRSE and MSSE did not show differences in their clinical presentation, but MRSE showed multidrug resistance including resistance to fluoroquinolone and tetracycline antibiotics.

FUNDING

None to declare

CONFICTS OF INTEREST

All the authors state no conflicts of interest

REFERENCES

1. Tena D, Rodríguez N, Toribio L, González-Praetorius A. Infectious keratitis: Microbiological review of 297 cases. Jpn J Infect Dis. 2019;72(2):121-23. doi: 10.7883/ yoken.JJID.2018.269.
2. Hernandez-Camarena JC, Graue-Hernandez EO, Ortiz-Casas M, Ramirez-Miranda A, Navas A, Pedro-Aguilar L, *et al.* Trends in microbiological and antibiotic sensitivity patterns in infectious keratitis: 10-year experience in Mexico City Cornea. 2015;34(7): 778-85. doi: 10.1097/ ICO.0000000000000428.
3. Mediero S, Boto de los Bueis A, Spiess K, Díaz-Almirón M, Del Hierro Zarzuelo A, Villalaín Rodes I, *et al.* Clinical and microbiological profile of infectious keratitis in an area of Madrid, Spain. Enferm Infecc Microbiol Clin. 2018;36(7):409-16. doi: 10.1016/ j.eimc.2017.08.002.
4. Sand D, She R, Shulman IA, Chen DS, Schur M, Hugo YH, *et al.* Microbial keratitis in Los Angeles: The doheny eye institute and the los angeles county hospital experience. Ophthalmology. 2015;122(5):918-24. doi: 10.1016/ j.ophtha.2014.11.027.
5. Durrani AF, Atta S, Bhat AK, Mammen A, Dhaliwal D, Kowalski RP, *et al.* Methicillin-Resistant *Staphylococcus aureus* Keratitis:

Initial Treatment, Risk Factors, Clinical Features, and Treatment Outcomes. Am J Ophthalmol. 2020; 214:119-26. doi: 10.1016 / j.ajo.2020.03.017.

6. Chang VS, Dhaliwal DK, Raju L, Kowalski PR. Antibiotic resistance in the treatment of *Staphylococcus aureus* Keratitis: A 20-year review. Cornea. 2015;34(6):698-703. doi: 10.1097/ ICO.0000000000000431.
7. Ong SJ, Huang YC, Tan HY, Ma DHK, Lin HC, Yeh LK, *et al. Staphylococcus aureus* keratitis: A review of hospital. PLoS One. 2013;8(11):6-11. doi: 10.1371/ journal.pone.0080119.
8. Peterson JC, Durkee H, Miller D, Maestre-Mesa J, Arboleda A, Aguilaret MC, *et al.* Molecular epidemiology and resistance profiles among healthcare- and community-associated *Staphylococcus aureus* keratitis isolates. Infect Drug Resist. 2019;12:831-43. doi: 10.2147/ IDR.S190245.
9. Goodman DF, Gottsch JD. Methicillin-Resistant *Staphylococcus epidermidis* Keratitis Treated with Vancomycin. Arch Ophthalmol. 1988;106(11):1570-71. doi: 10.1001/archopht.1988.01060140738046.
10. Tabbara KF, Antonios S, Alvarez H. Effects of fusidic acid on staphylococcal keratitis. Br J Ophthalmol. 1989;73(2):136-39. doi: 10.1136/bjo.73.2.136.
11. Kitazawa K, Sotozono C, Sakamoto M, Sasaki M, Hieda O, Yamasaki T, *et al.* Nasal and conjunctival screening prior to refractive surgery: An observational and cross-sectional study. BMJ Open. 2016;6(5):1-6. doi: 10.1136/bmjopen-2015-010733.
12. Lin YH, Kang YC, Hou CH, Huang YC, Chen CJ, Shu JC, *et al.* Antibiotic susceptibility profiles of ocular and nasal flora in patients undergoing cataract surgery in Taiwan: An observational and cross-sectional study. BMJ Open. 2017;7(8):1-8. doi: 10.1136/bmjopen-2017-017352.
13. Xu Z, Cave R, Chen L, Yangkyi T, Liu Y, Liet K, *et al.* Journal of Global Antimicrobial Resistance Antibiotic resistance and molecular characteristics of methicillin-resistant *Staphylococcus epidermidis* recovered from hospital personnel in China. 2020;22:195-201. doi: 10.1016/j.jgar.2020.02.013.
14. Stewart PS. Mechanisms of antibiotic resistance in bacterial biofilms. Int J Med Microbiol. 2002;292(2):107-13. doi: 10.1078/1438-4221-00196.
15. Eghrari AO, Riazuddin SA, Gottsch JD. Overview of the Cornea: Structure, Function, and Development. Vol 134. 1st ed. Elsevier Inc.; 2015. doi: 10.1016/bs.pmbts.2015.04.001.
16. Hori J, Yamaguchi T, Keino H, Hamrah P, Maruyama K. Immune privilege in corneal transplantation. Prog Retin Eye Res. 2019;72(January):100758. doi: 10.1016/j.preteyeres.2019.04.002.
17. Lin A, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, *et al.* Bacterial Keratitis Preferred Practice Pattern. Ophthalmology. 2019;126(1):P1-P55. doi: 10.1016/j.ophtha.2018.10.018.
18. Dave SB, Toma HS, Kim SJ. Ophthalmic antibiotic use and multidrug-resistant *Staphylococcus epidermidis*: A controlled, longitudinal study. Ophthalmology. 2011;118(10):2035-40. doi: 10.1016/j.ophtha.2011.03.017.
19. George JM, Fiscella R, Blair M, Rodvold K, Ulanski L, Stokes J, *et al.* Aqueous and vitreous penetration of linezolid and levofloxacin after oral administration. J Ocul Pharmacol Ther. 2010;26(6):579-86. doi: 10.1089/jop.2010.0022.
20. Papa V, Blanco AR, Santocono M. Ocular flora and their antibiotic susceptibility in patients having cataract surgery in Italy. J Cataract Refract Surg. 2016;42(9):1312-17. doi: 10.1016/j.jcrs.2016.07.022
21. Lee JYH, Monk IR, Gonçalves da Silva A, Seemann T, Chua KYL, Kearns A, *et al.* Global spread of three multidrug-resistant lineages of *Staphylococcus epidermidis*. Nat Microbiol. 2018;3(10):1175-85. doi: 10.1038/ s41564-018-0230-7
22. Liu C, Chen C, Ye Y, Li X, Sun J, Xuet L, *et al.* The emergence of *Staphylococcus epidermidis* simultaneously nonsusceptible to linezolid and teicoplanin in China. Diagn Microbiol Infect Dis. 2020;96(2):114956. doi 10.1016/j.diagmicrobio.2019.114956

Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/132.2021

Azucena Bautista Hernández[1]
Enrique de Vega-Ríos[1]
Jorge Serrano Ballesteros[1]
Daniel Useros Braña[1]
Laura Cardeñoso Domingo[2]
Angels Figuerola Tejerina[3]
Andrés von Wernitz Teleki[4]
David Jiménez Jiménez[5]
Ignacio de los Santos Gil[1]
Carmen Sáez Béjar[1]

Impact of the implementation of a Sepsis Code Program in medical patient management: a cohort study in an Internal Medicine ward

[1]Internal Medicine and Infectious Diseases Department. Hospital de la Princesa, IIS-IP, Madrid, Spain.
[2]Microbiology department, Hospital de la Princesa, IIS-IP, Madrid, Spain.
[3]Preventive Medicine department, Hospital de la Princesa, IIS-IP, Madrid, Spain.
[4]Emergency department, Hospital de la Princesa, IIS-IP, Madrid, Spain.
[5]Intensive Care department. Hospital de la Princesa, IIS-IP, Madrid, Spain.

Article history
Received: 19 September 2021; Revision Requested: 5 October 2021; Revision Received: 5 October 2021; Accepted: 4 November 2021; Published: 31 January 2022

ABSTRACT

Introduction. Sepsis is the main cause of death in hospitals and the implementation of diagnosis and treatment bundles has shown to improve its evolution. However, there is a lack of evidence about patients attended in conventional units.

Methods. A 3-year retrospective cohort study was conducted. Patients hospitalized in Internal Medicine units with sepsis were included and assigned to two cohorts according to Sepsis Code (SC) activation (group A) or not (B). Baseline and evolution variables were collected.

Results. A total of 653 patients were included. In 296 cases SC was activated. Mean age was 81.43 years, median Charlson comorbidity index (CCI) was 2 and 63.25% showed some functional disability. More bundles were completed in group A: blood cultures 95.2% vs 72.5% ($p < 0.001$), extended spectrum antibiotics 59.1% vs 41.4% ($p < 0.001$), fluid resuscitation 96.62% vs 80.95% ($p < 0.001$). Infection control at 72 hours was quite higher in group A (81.42% vs 55.18%, odds ratio 3.55 [2.48-5.09]). Antibiotic was optimized more frequently in group A (60.77% vs 47.03%, p 0.008). Mean in-hospital stay was 10.63 days (11.44 vs 8.53 days, $p < 0.001$). Complications during hospitalization appeared in 51.76% of patients, especially in group B (45.95% vs 56.58%, odds ratio 1.53 [1.12-2.09]). Hospital readmissions were higher in group A (40% vs 24.76%, $p < 0.001$). 28-day mortality was significantly lower in group A (20.95% vs 42.86%, odds ratio 0.33 [0.23-0.47]).

Conclusions. Implementation of SC seems to be effective in improving short-term outcomes in IM patients, although therapy should be tailored in an individual basis.

Keywords: Sepsis, Internal Medicine, short-term mortality, complications, readmissions

Correspondence:
Azucena Bautista Hernández
Internal Medicine Clinician, Hospital Universitario de La Princesa.
C/Diego de León, 62 – 28006. Madrid, Spain.
E-mail: bautistazucena@gmail.com

Impacto de la implementación del Programa Código Sepsis en una planta de hospitalización médica: estudio de una cohorte de pacientes de Medicina Interna

RESUMEN

Introducción. La sepsis es la principal causa de muerte en los hospitales y la implantación de códigos para su manejo ha demostrado mejorar su evolución. Sin embargo, es escasa la evidencia relativa a los pacientes atendidos en unidades médicas convencionales.

Métodos. Se realizó un estudio de cohortes retrospectivo de 3 años. Se incluyeron pacientes con sepsis hospitalizados en unidades de Medicina Interna y se asignaron a dos cohortes según la activación del Código Sepsis (CS) (grupo A) o no (B). Se recogieron variables basales y de evolución.

Resultados. Se incluyeron 653 pacientes. En 296 casos se activó el SC. La edad media fue de 81,43 años, la mediana del índice de comorbilidad de Charlson (ICC) fue de 2 y el 63,25% presentaba alguna limitación funcional. Se realizaron más acciones diagnósticas y terapéuticas en el grupo A: hemocultivos 95,2% vs 72,5% (p < 0,001), antibióticos de espectro extendido 59,1% vs 41,4% (p < 0,001), reanimación con líquidos 96,62% vs 80,95% (p < 0,001). El control de la infección a las 72 horas fue superior en el grupo A (81,42% vs 55,18%, odds ratio 3,55 [2,48-5,09]). La optimización de los antibióticos fue más frecuente en el grupo A (60,77% vs 47,03%, p 0,008). La estancia media en el hospital fue de 10,63 días (11,44 vs 8,53 días, p < 0,001). Aparecieron complicaciones durante la hospitalización en el 51,76% de los pacientes, especialmente en el grupo B (45,95% vs 56,58%, odds ratio 1,53 [1,12-2,09]). Los pacientes del grupo A reingresaron más (40% vs 24,76%, p < 0,001). La mortalidad a los 28 días fue significativamente menor en el grupo A (20,95% frente a 42,86%, odds ratio 0,33 [0,23-0,47]).

Conclusiones. La aplicación del CS parece ser eficaz para

mejorar los resultados a corto plazo en los pacientes de MI, aunque el tratamiento debe adaptarse de forma individual.

Palabras clave: Sepsis, Medicina Interna, mortalidad corto plazo, complicaciones, reingresos

INTRODUCTION

Sepsis is the leading cause of death in hospitals in Spain and its incidence and mortality is constantly increasing in developed countries [1–7]. The fatality rate associated with sepsis is higher than 10% and higher than other serious medical entities, reaching 40% in cases of septic shock [1,2].

Prognosis of sepsis and septic shock is related to the time elapsed between the onset of symptoms and the administration of antibiotics and fluid resuscitation [5,8]. In recent decades, various initiatives have shown that early and organized detection and treatment of sepsis, reduce mortality by up to 50% (3,4,9,10]. In our country, the Sepsis code protocol (SCP) has been endorsed by the main scientific societies [11,12]. In this context, a multidisciplinary team was formed in our hospital in 2013. Its objective was to develop, promote and update a protocol to improve the prognosis of patients with sepsis, not only those admitted to the Intensive Care Unit (ICU), but also patients in conventional wards. Our guide established some key elements for sepsis management, focusing on diagnosis, biomarkers and therapy. It was based on the compendium of recommendations or bundles published by the Surviving Sepsis Campaign [9,13], among others. This SC initiative was implemented in the hospital´s clinical practice in 2015

Most of the evidence on the impact of these early detection and management packages on sepsis patients comes from those hospitalized in the ICU [1–5]. This group of individuals usually share some characteristics such as age under 80 years, preserved functional capacity and absence of severe baseline comorbidity that could determine their survival prognosis. However, the clinical setting in conventional hospital units is different, especially in the case of Internal medicine (IM): the range of patients is broader including those with greater comorbidity, age or functional dependence [14,15]. Currently, there is limited evidence on how bundles affect the clinical course of these patients, who account for at least 50% of sepsis diagnoses in hospitals [16,17]. Furthermore, despite protocol implementation, we identify a significant number of patients in whom the code is not activated at the time of sepsis diagnosis. We think it could be related to a worse baseline situation due to relevant comorbidities or cognitive impairment. In addition, literature has recently emerged offering contradictory findings about potential negative impact of implementing certain aspects of the SCP such as excessive or rigid fluid resuscitation [18–22]. Therefore, we considered it necessary to develop a research line to explore the best management options for this hugely diverse group of patients.

Accordingly, the main aim of this study was to evaluate the impact of the Sepsis Code (SC) on the morbidity and mortality of sepsis patients outside the ICU to identify potentially improvable points. The SC program included the main recommendations of the current SSC guidelines [9] regarding the diagnosis, treatment and follow-up of sepsis. For that purpose, we describe and analyze, in patients hospitalized at the IM ward, the baseline and evolutionary differences between patients managed with and without activated SC.

PATIENTS AND METHODS

Patients. This was a retrospective study conducted at the IM unit of Hospital Universitario de La Princesa (HULP), a tertiary teaching center in Madrid (Spain), from January 2016 to December 2018. The entire hospital has roughly 15000 admissions per year and the IM Department around 2200. This study was approved by the Research ethics Committee of the hospital (protocol number: 3703).

All patients hospitalized at the IM ward as the first location and with a diagnosis, in the clinical discharge report, of sepsis or any septic-related presentation according to ICD-10-CM [23] were eligible. We checked if the SC alert had been activated in those patients hospitalized in MI during the study period. For this purpose, the documentation department has a list of all historically activated alerts in the hospital. The sample was divided into two cohorts according to whether SC was activated (A) or not (B). The only exclusion criterion was to have been initially admitted to other department. In addition, we included in cohort A those patients who lacked a sepsis or related diagnosis in the discharge report but were managed with an activated SC during hospitalization. The diagnosis and treatment protocol in cohort A was based on the bundles recommended in the current SSC guidelines [9] and on usual care in cohort B.

Data collection. The following baseline demographic and clinical characteristics collected from the medical information system were included: age, gender, comorbidities, immunosuppression, risk factors for developing a multidrug-resistant bacterial (MDRB) or a fungal infection, presence and type of devices, functional capacity, site of infection, presence of third space enlargement defined as pleural effusion, leg edema or ascites, and evidence of some abscess. All of them referred to the situation at the time of hospital admission, which usually coincided with sepsis diagnosis. Comorbidity burden was assessed using the Charlson comorbidity index (CCI). We considered relevant comorbidity if CCI was >3 as previous reports [24–27]. Functional capacity was evaluated using the Barthel Index (BI) [28,29] and was classified into three ranges: independence ≥ 99 points, partial dependence 30-98 points and severe dependence ≤ 29 points.

The type, number, and time of sampling for the microbiology laboratory were reviewed. Also, variables related to antibiotic treatment, surgical or interventionist control of the infectious site, fluid resuscitation, vasopressors, blood transfusions, and corticoid therapy were collected. Data on time to fluid resuscitation from diagnosis of sepsis and activation of SC were only available for patients in group A.

Outcome measures. The primary outcome was 28-day mortality rate. Other outcomes included were: 1) controlled infection within 72 hours from diagnosis, defined as the absence of fever, hemodynamic stability and improvement of acute phase reactants (drop in leukocytes, C-reactive protein or procalcitonin), 2) overall length of the stay, 3) in-hospital complications; 4) detrimental effects of antibiotic, 5) readmission within the following 12 months and its causes, and 6) in-hospital and long-term mortality (at 365 days).

Statistical analysis. Results are expressed as means and standard deviation (SD), medians and interquartile range (IQR), or proportions with 95% confidence intervals (CI) as appropriate. χ^2 test or Fisher´s exact test were used to compare categorical variables and Student´s *t*-test or Mann-Whitney U test to compare continuous variables. The cumulative incidence of mortality was estimated using the Kaplan-Meier method and compared using the log-rank test. We examined factors associated with outcomes by conducting logistic regression. All statistical analyses were performed using SPSS software (version 25). Two- tailed *p* values ≤ 0.05 were considered statistically significant.

RESULTS

Baseline characteristics. A total of 653 patients out of 6.676 admitted to the IM ward during the study period were included, as shown Figure 1. Of them, 564 patients were diagnosed with sepsis or any related form in the medical discharge report, while 89 patients did not have sepsis diagnosis but were managed with activated SC. The total of diagnosed patients was divided into two cohorts according to whether the SC was activated (cohort A, 296 patients) or not (cohort B, 357 patients).

Patients in cohort B were older (83.05 vs 79.32 years, p =0.001) and their functional status was worse than those in cohort A (severe dependent patients 41.46% vs 27.36%, $p <$ 0.001). The presence of comorbidity and the distribution of infection foci did not differ between cohorts, whereas the presence of third space enlargement was numerically greater in cohort B (p=0.056).

Characteristics of microbiological diagnosis and treatment. The differences in timing and details of sample collection for microbiological diagnosis are summarized in Table 2. More samples were collected in cohort A (98.31% vs

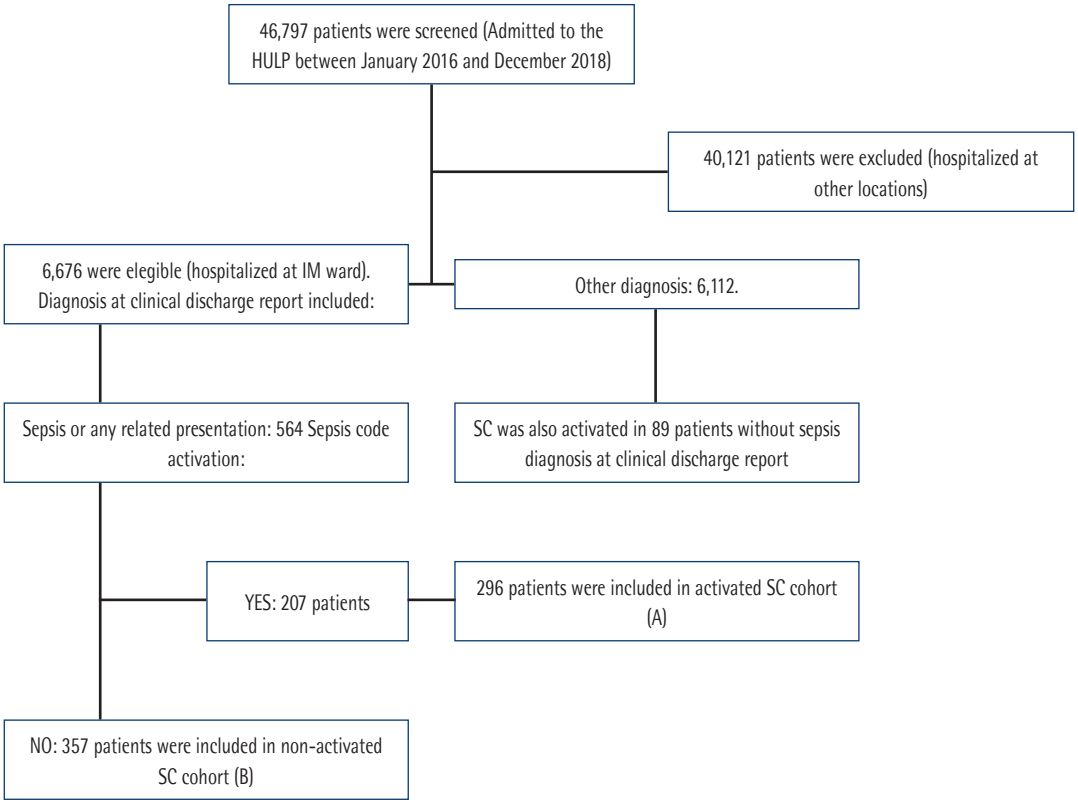


Figure 1 | **Study flowchart.**

HULP: Hospital Universitario de la Princesa; IM: Internal Medicine; SC: Sepsis Code

Table 1 **Baseline and clinical characteristics.**

Baseline and clinical characteristics	TOTAL n=653	SC activated (A) n=296	SC not activated (B) n=357	p
Age, years mean (SD)	81.43 (14.60)	79.32 (15.31)	83.05 (13.78)	**0.001**
Male sex, n (%)	311	160 (54.05)	151 (42.3)	**0.003**
Charlson comorbidity index, median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	0.11
Charlson comorbidity index >3, n (%)	283 (43.3)	119 (40.2)	164 (45.9)	0.141
Inmmunosuppression, n (%)	74 (11.33)	41 (13.85)	33 (9.24)	0.064
Risk factors for multi-resistant bacterial infection, n (%)	298 (45.64)	152 (51.35)	146 (40.9)	**0.008**
Risk factors for fungal infection, n (%)	153 (23.43)	80 (27.03)	73 (20.45)	**0.048**
Device carrier, n (%)	74 (11.3)	36 (12.2)	38 (10.6)	0.542
Type of device, n (%)				0.321
Bladder catheter	55 (74.3)	25 (69.4)	30 (78.9)	
Another urinary catheter	6 (8.1)	2 (5.6)	4 (10.5)	
Nasogastric tube	9 (12.2)	7 (19.4)	2 (5.3)	
Digestive endoprosthesis	2 (2.7)	1 (2.8)	1 (2.6)	
Both, bladder catheter and nasogastric tube	1 (1.4)	1 (2.8)	0 (0)	
Ventriculoperitoneal system	1 (1.4)	0 (0)	1 (2.6)	
Functional capacity, n (%)				**0.001**
Independence	240 (36.75)	124 (41.89)	116 (32.49)	
Partial dependence	184 (28.18)	91 (30.74)	93 (26.05)	
Severe dependence	229 (35.07)	81 (27.36)	148 (41.46)	**< 0.001**
Suspected site of infection, n (%)				0.189
Neurologic	4 (0.61)	2 (0.64)	2 (0.56)	
Pulmonary	219 (33.54)	93 (31.42)	126 (35.29)	0.296
Urinary tract	258 (39.51)	112 (37.84)	146 (40.9)	0.426
Both, pulmonary and urinary tract	34 (5.21)	13 (4.39)	21 (5.88)	
Abdominal	36 (5.5)	19 (6.4)	17 (4.8)	
Soft tissue	49 (7.5)	24 (8.1)	25 (7)	
Intravascular	3 (0.5)	3 (1)	0	
Surgical site	1 (0.2)	0 (0)	1 (0.3)	
Orthopedics	12 (0.3)	1 (0.3)	1 (0.3)	
Unknown site	47 (7.2)	29 (9.8)	18 (5)	
Concordance between suspected and confirmed infection site, n (%)	515 (78.9)	228 (77)	287 (80.4)	0.294
Third space enlargement, n (%)	52 (7.96)	17 (5.74)	35 (9.8)	0.056
Abscess, n (%)	39 (5.97)	14 (4.73)	25 (7)	0.248

Significant *p* values (≤ 0.05) are highlighted in bold. Abbreviations: IQR, interquartile range; SC, Sepsis Code; SD, standard deviation

82.07%, p < 0.001), especially blood samples (95.2% vs 72.5%, *p* < 0.001). On the contrary, urine culture was more frequently collected in cohort B (*p* 0.015).

Regarding treatment, extended-spectrum antibiotic was more frequent in group A (59.1% vs 41.4%, *p* < 0.001) and antibiotic treatment was also changed more frequently in this cohort (61.1 vs 53.5%, *p* 0.046), especially in relation to microbiological results (60.77% vs 47.03%, *p* 0.008). There were also significant differences in the number of patients who received

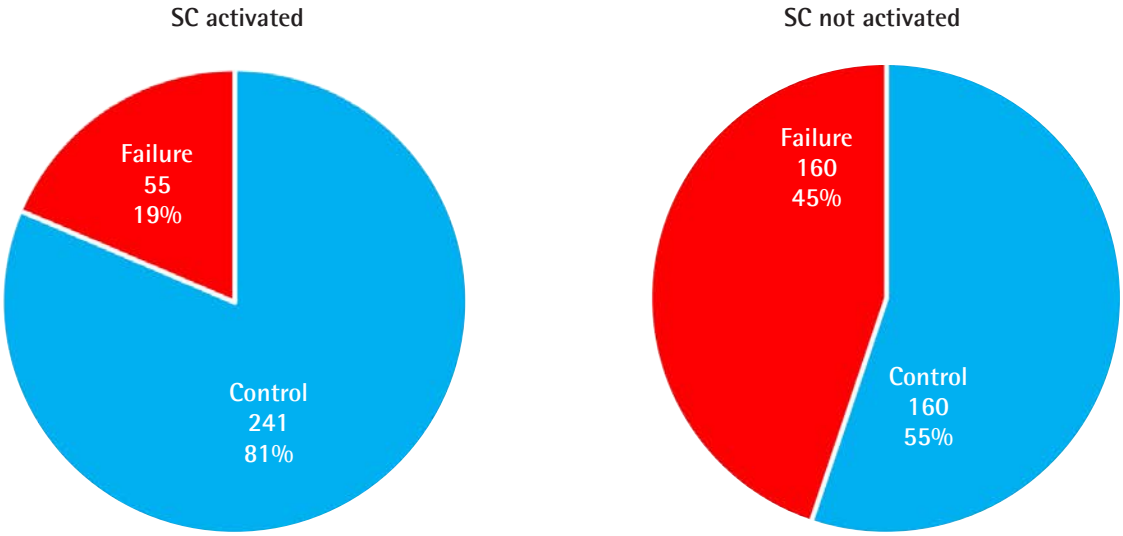


Figure 2 | **Infection status within 72 hours from diagnosis. Data are expressed as n and % in the two cohorts.**

SC: Sepsis Code.

fluid resuscitation (96.62% vs 80.95%, $p < 0.001$) and vasopressors (12.88% vs 1.4%, $p < 0.001$). Time to fluid resuscitation in group A was less than 1 hour in 268 patients (93.71%).

Clinical evolution. Sepsis was controlled within 72 hours in 81.42% of patients in cohort A in contrast to 55.18% in cohort B (OR 3.55, 95% CI 2.48-5.09, $p < 0.001$) as shown in Figure 2.

Patients with activated SC stayed longer in hospital (11.44 days vs 8.53 days, $p < 0.001$) and received longer-lasting antibiotic treatments (12.46 days vs 8.26 days, p=0.003). However, time to narrow the spectrum of antibiotics was longer in cohort B (2.31 days vs 4.13 days, p=0.017). No differences in the time to hospital readmission could be found between the two cohorts (Table 3).

Complications during hospitalization are summarized in Table 4 and Figure 3. Remarkably, overall number of complications was higher in cohort B (45.95% vs 56.58%, OR 1.53, 95% CI 1.12-2.09, p 0.007), as well as acute renal failure (0.7% vs 6.4%, OR 0.09 95% CI 0.02-0.42, $p < 0.001$) and others globally (10.1% vs 32.2%, OR 0.23 95% CI 0.15-0.36, $p < 0.001$). Conversely, the incidence of heart failure and acute confusional episodes was significantly higher in cohort A (27.36% vs 19.05 and 47.2% vs 27.2% $p < 0.001$, respectively).

Side effects after antibiotic treatment are shown in Table 5 and Figure 4. No statistically significant differences in the appearance of toxicity could be found between cohorts, whereas the incidence in the following year of infections by MDRB was higher in cohort B (OR 0.15, 95% CI 0.03-0.76, p 0.012). However, readmissions were more frequent in cohort A (OR 2.02, 95% CI 1.36-2.99, p < 0.001) and the leading cause was another infection or sepsis (Table 6).

Mortality. Mortality information is shown in Figure 5. 28-day and in-hospital mortality were lower in cohort A (18.92% vs 37.54%, OR 0.39 95% CI 0.27-0.55, p <0.001 and 20.95% vs 42.86%, OR 0.23-0.47 95% CI 0.23-0.47, $p < 0.001$, respectively). Conversely, at 365 days mortality reached 58.8% in cohort A vs 40.3% in B (OR 1.5 95% CI 1.00-2.25, p 0.045). Differences between 28-day survival curves are shown in Figure 6. Highlights the difference in mortality especially in the short term.

DISCUSSION

Baseline characteristics and sepsis diagnosis. Patients in our sample had an overall average age higher than that referred in the European series (around 70-75 years) [30–32]. The difference is even greater compared with cohort B. Our average age can be compared with that shown by Vardi et al. [33] and Liu et al. [34], from their elderly subgroup.

Regarding comorbidities, the overall median CCI and the percentage of patients with immunosuppression, did not differ between cohorts and were similar to those of reference series [33,35]. It is notable that half of patients had risk factors for MDRB infection. More than half had a deteriorated functional status and a third showed severe deterioration. There are significant differences between groups, with a worse functional status in no-SC group. We consider that this could be one of the criteria (along with age) for SC activation, since the rest of the baseline characteristics are similar in both groups.

Most infections appeared at the pulmonary and urinary tracts in both cohorts and showed a low rate of abscesses, pre-

Table 2 **Characteristics of microbiological diagnosis and treatment.**

Microbiological diagnosis and treatment	Total	SC activated (A)	SC not activated (B)	p
Samples collected for microbiology, n (%)	584 (89.13)	291 (98.31)	293 (82.07)	**< 0.001**
At least two different samples collected, n (%)	448 (68.61)	255 (86.15)	193 (54.06)	**< 0.001**
Blood sample, n (%)	488 (83.8)	277 (95.2)	211 (72.5)	**< 0.001**
Urine sample, n (%)	398 (68.3)	185 (63.6)	213 (72.9)	**0.015**
Abdominal exudate or drainage, n (%)	16 (2.7)	8 (2.7)	8 (2.7)	1,000
Other samples, n (%)				0.397
Respiratory tract exudate	50 (64.9)	6 (66.7)	44 (64.7)	
Soft tissue sample	15 (19.5)	1 (11.1)	14 (20.6)	
Cerebrospinal fluid	5 (6.5)	0	5 (7.4)	
Stool sample	7 (9.1)	2 (22.2)	5 (7.4)	
Collection previous to antibiotic administration, n (%)	496 (84.93)	251 (86.25)	245 (83.62)	0.214
Extended spectrum antibiotic administration, n (%)	317 (49.6)	175 (59.1)	142 (41.4)	**< 0.001**
Combination antibiotic therapy, n (%)	444 (69.5)	153 (51.7)	291 (84.8)	**< 0.001**
Intravenous antibiotic administration, n (%)	634 (99.4)	294 (99.7)	340 (99.1)	0.393
Surgical or interventionist therapy n (%)	25 (3.8)	10 (3.4)	15 (4.2)	0.585
Antibiotic adjustment during evolution, n (%)	366 (56.90)	181 (61.1)	185 (53.3)	0.046
Spectrum of coverage narrowed, n %)	221 (34.4)	140 (47.3)	81 (23.3)	**< 0.001**
Optimization of therapy based on microbiological results, n (%)	197 (53.83)	110 (60.77)	87 (47.03)	**0.008**
Other reasons for tailoring antibiotic, n (%)				**0.025**
Empirical optimization based on clinical practice guidelines	90 (53.25)	45 (63.38)	45 (45.92)	
Empirical optimization due to clinical failure	79 (46.75)	26 (36.6)	53 (54.1)	
Switch to oral antibiotic, n (%)	278 (43.23)	165 (55.74)	113 (32.56)	**< 0.001**
Fluid resuscitation, n (%)	575 (88.06)	286 (96.62)	289 (80.95)	**< 0.001**
Fluid choice, n (%)				0.371
Crystalloid	570 (99.13)	283 (98.95)	287 (99.31)	
Colloid	1 (0.17)	0	1 (0.35)	
Both, crystalloid and colloid	4 (0.70)	3 (1.05)	1 (0.35)	
Vasopressor use, n (%)	43 (6.6)	38 (12.88)	5 (1.4)	**< 0.001**
Vasopressor choice, n (%)				**0.002**
Dopamine	33 (71.74)	30 (78.95)	3 (37.5)	
Dobutamine	3 (6.52)	0 (0)	3 (37.5)	
Noradrenaline	9 (19.57)	7 (18.42)	2 (25)	
Phenylephrine	1 (2.17)	1 (2.63)	0 (0)	
Blood transfusion, n (%)	21 (3.23)	13 (4.42)	8 (2.25)	0.119
Corticoid therapy, n (%)	64 (9.83)	32 (10.88)	32 (8.96)	0.413

Time to fluid resuscitation is only shown for group A, because the exact time of sepsis onset in group B was unknown. Significant *p* values (≤0.05) are highlighted in bold. Abbreviations: SC, Sepsis Code

Table 3 **Quantitative variables.**

Quantitative variables	Total	SC activated (A)	SC not activated (B)	p
Length of hospital stay in days, mean (SD)	8.51 (10.63)	12.63 (11.44)	5.10 (8.53)	**< 0.001**
Length of ICU stay in days, mean (SD)	8.5 (6.86)	6.2 (4.32)	10.14 (8.15)	0.350
Total duration of antibiotic treatment in days, mean (SD)	11.55 (10.36)	12.77 (12.46)	10.29 (8.26)	**0.003**
Time to reduce antibiotic spectrum coverage in days, mean (SD)	4.35 (3.21)	3.88 (2.31)	5.04 (4.13)	**0.017**
Time to switch from intravenous to oral antibiotic in days, mean (SD)	6.46 (5.21)	6.88 (5.54)	5.93 (4.75)	0.117
Time to hospital readmission in days, mean (SD)	105.98 (97.89)	103.46 (97.77)	107.85 (98.53)	0.741
Time to hospital readmission in days, median (IQR)	64.88 (30.41-152.08)	64.88 (32.44-151.06)	64.38 (30.41-154.87)	0.903

Significant *p* values (≤0.05) are highlighted in bold. Abbreviations: ICU, Intensive Care Unit; IQR, interquartile range; SD, standard deviation; SC, Sepsis Code.

dictably in medical patients and similar to published evidence [35–37].

Microbiological diagnosis and treatment. Microbiological diagnosis efforts were significantly different in both groups: samples were more frequently collected in group A, and the number of samples, specifically blood samples were also superior in this cohort while urine culture were more frequently obtained in group B, probably reflecting the "less invasive" attitude in the second group. This finding has important implications for the correct antibiotic treatment and may affect the control and evolution of the infection [38–40]. The compliance with the diagnostic sepsis bundles in cohort A are considerably better than those described in previous series (20-50%). [3,36,41,42].

Antibiotic and fluid therapy were administered in a similar proportion than described in previous studies in ICU patients (63-100%), whereas the proportion of vasopressor or steroid administration was lower [27-100% and 29.9-70%, respectively) [3,4,41] as expected in conventional wards.

Extended spectrum antibiotics (ESA) were more frequently administered in cohort A. We found that these patients had more risk factors for MDRB at admission. Although combined therapy was more common in group B maybe reflecting the need for achieving the same coverage with narrower spectrum drugs. Antibiotic therapy was adjusted to microbiological results in more cases in group A and time to reduce antibiotic spectrum coverage was shorter. Moreover, antibiotic treatment was switched to oral route more frequently, though not earlier. Nevertheless, we observed a higher mean duration of total antibiotic treatment in group A. Similar length in the context of SCP implementation is shown in other series in our country (a mean of 10.9 days in Pinilla et al. [43] and 13 days in García-López et al. [44]). Furthermore, it has been suggested that antibiotic stewardship programs do not reduce total duration of therapy [40,45,46] and there is an increasing evidence showing that an early antibiotic de-escalation based on microbiological results provides similar survival and outcomes to those of a longer and extended treatment regimen [22,39,40,47,48]. Therefore, it seems that antibiotic treatment is generally more appropriate in the SC group, although the time to narrow spectrum could be improved. In our study, group B developed more infections due to MDRB during the following year, and this could be related to suboptimal antibiotic de-escalation [49].

A higher number of patients were treated with fluid resuscitation and vasopressors in group A according to SCP recommendations. In both, the main choice were crystalloids and dopamine, respectively. We found no differences in blood transfusion or corticosteroid therapy between groups.

Clinical evolution. The probability of controlling infection after 72 hours of treatment was almost 4 times higher in SC group. We found no published evidence regarding concrete information on early clinical improvement status after SCP implementation. Infection control is directly related to improving prognosis and short-term mortality [3,4,9,50]. In our population, complications were frequently observed, in more than 50% of patients, similar to that described by Vardi et al. [33]. The risk of complications is 1.5 higher in group B. Global length of stay was similar to other reports [4,37,42]. Treatment was more intensive in group A especially fluid resuscitation and it could be the reason for the higher incidence of heart failure. Acute confusional syndrome was also higher in group A. We think that it could be explained by longer reality deprivation. On the contrary, renal failure and others were more frequent in group B, probably related to this "less invasive" management. These findings widely support the opinion of other authors regarding the flexibility of the management recommendations in some frail patients, adapting them to their individual basis [18,19,21,22,51].

Finally, almost a third of survivors were readmitted within 12 months. The probability of readmission is twice more frequent in group A. The mean time to readmission was similar in both groups. Half of them occurred in the first 3 months after discharge, which may suggest that they were related to complications of sepsis and its treatment. Readmission rates and causes within the first 90 days after discharge were similar to

Table 4 **In-hospital complications.**

In-hospital complications	TOTAL	SC activated (A)	SC not activated (B)	OR	95% CI	p
Complication outcomes, n (%)	338 (51.76)	136 (45.95)	202 (56.58)	1.53	1.12-2.09	**0.007**
Heart failure, n (%)	149 (22.82)	81 (27.36)	68 (19.05)	1.6	1.10-2.31	**0.012**
Phlebitis associated to intravenous catheters, n (%)	24 (3.68)	9 (3.04)	15 (4.2)	0.75	0.30-1.65	0.432
Acute renal failure, n (%)	25 (3.8)	2 (0.7)	23 (6.4)	0.09	0.023-0.423	**< 0.001**
Acute confusional syndrome, n (%)	50 (34.5)	25 (47.2)	25 (27.2)	2.39	1.17-4.85	**0.015**
Others, n (%)	145 (22.2)	30 (10.1)	115 (32.2)	0.23	0.15-0.36	**< 0.001**
Non-clostridial diarrhea	4 (4.3)	3 (10.7)	1 (1.6)			
Mucocutaneous candidiasis	6 (6.5)	2 (7.1)	4 (6.3)			
Coagulopathy or other bleeding diathesis	1 (1.1)	1 (3.6)	0			
Thrombocytopenia	1 (1.1)	0	1 (1.6)			
Anaemia	5 (5.4)	0	5 (7.8)			
Electrolyte disorder	7 (7.6)	2 (7.1)	5 (7.8)			
Coronary syndrome	3 (3.3)	1 (3.6)	2 (3.1)			
Cardiac arrhythmia	3 (3.3)	0	3 (4.7)			
Seizures	1 (1.1)	0	1 (1.6)			
Acute urinary retention	9 (9.8)	3 (10.7)	6 (9.4)			
At least two of the above	52 (56.5)	15 (53.6)	37 (57.8)			
ICU admission due sepsis or any complication, n (%)	10 (1.53)	7 (2.36)	3 (0.84)			0.198

Significant *p* values (≤0.05) are highlighted in bold. Abbreviations: CI, confidence interval; ICU, Intensive Care Unit; OD, odds ratio; SC, Sepsis Code.

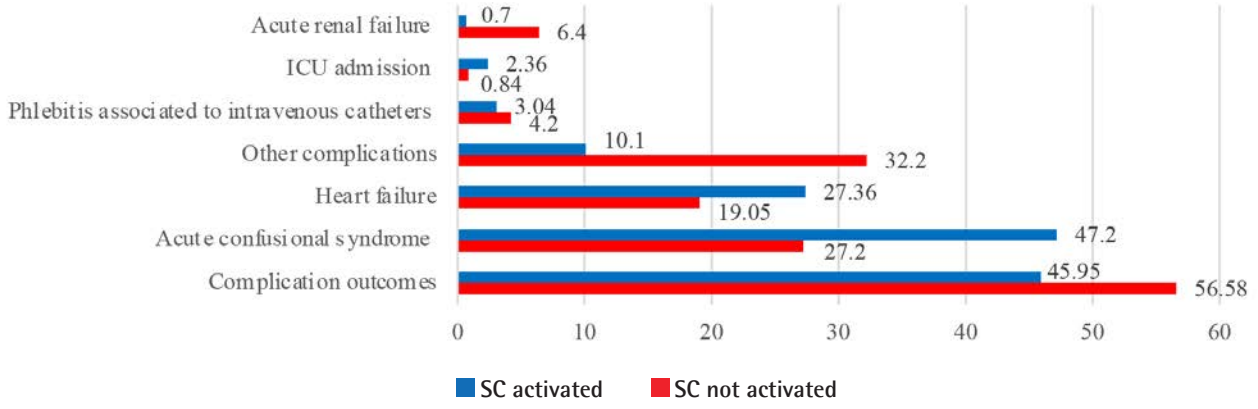


Figure 3 **In-hospital complications. Data are expressed as percentages in the two cohorts.**

SC: Sepsis Code.

those reported in previous studies [52–54]. Study population was frail, comorbid and at high risk of readmission. Lower early mortality in SC group may be the main cause of readmission. Furthermore, data do not suggest readmissions were linked to treatment complications, but rather to a new sepsis episode.

Mortality. In the present study overall 28-day mortality rate in sepsis patients admitted to the IM ward was 32%, similar to that described in studies that also included patients admitted to the ICU [3,4,16,17,36,37]. Focusing on the specific data from general wards, in these studies the percentages

Table 5 **Antibiotic related complications or side effects.**

Antibiotic related complications or side effects	TOTAL	SC activated (A)	SC not activated (B)	OR	95% CI	p
Toxicity, n (%)	43 (6.6)	16 (5.4)	27 (7.6)	0.69	0.36-1.32	0.268
Type of toxicity, n (%)						0.076
Hypersensitivity reactions	0	0	0			
Dermatologic reactions	5 (11.4)	2 (12.5)	3 (10.7)			
Neurotoxicity	5 (11.4)	0	5 (17.9)			
Gastrointestinal	9 (20.5)	3 (18.8)	6 (21.4)			
Hepatic	13 (29.5)	3 (18.8)	10 (35.7)			
Renal	6 (13.6)	5 (18.8)	10 (35.7)			
Hematologic	5 (11.4)	2 (12.5)	3 (10.7)			
Rhabdomyolysis	1 (2.3)	1 (6.3)	0			
Severe toxicity, n (%)	5 (11.6)	0	5 (18.5)	1.22	1.02-1.46	0.067
Multidrug-resistant bacterial colonization, n (%)	66 (10.14)	33 (11.15)	33 (9.3)	1.23	0.74-2.05	0.421
Multidrug-resistant bacterial infection, n (%)	53 (81.5)	23 (69.7)	30 (93.8)	0.15	0.03-0.76	**0.012**
Colonization/infection diagnostic culture 1, n (%)						**< 0.001**
Blood culture	9 (13.6)	0	9 (27.3)			
Urine culture	38 (57.6)	19 (57.6)	19 (57.6)			
Respiratory tract culture	10 (15.2)	10 (30.3)	0			
Soft tissue exudate culture	8 (12.1)	4 (12.1)	4 (12.1)			
Cerebrospinal fluid culture or analysis	1 (1.5)	0	1 (3)			
Isolated microorganism in culture 1, n (%)						0.576
Methicillin-resistant *Staphylococcus aureus*	6 (9.1)	2 (6.1)	4 (12.1)			
Linezolid-resistant coagulase-negative staphylococci	1 (1.5)	0	1 (3)			
Ampicillin and vancomycin-resistance enterococci	2 (3)	1 (3)	1 (3)			
Enterobacteriaceae producing ESBL, AmpC BL and carbapenemases	2 (3)	2 (6.1)	0			
Multidrug-resistant *Pseudomonas aeruginosa*	6 (9.1)	3 (9.1)	3 (9.1)			
Another multidrug-resistant microorganism	1 (1.5)	0	1 (3)			
Clostridioides difficile	0	0	0			
Colonization/infection diagnostic culture 2, n (%)						**0.027**
Urine culture	3 (16.7)	2 (50)	1 (7.1)			
Respiratory tract culture	10 (55.6)	0	10 (71.4)			
Soft tissue exudate culture	5 (27.8)	2 (50)	3 (21.4)			
Isolated microorganism in culture, n (%)						0.825
Methicillin-resistant *Staphylococcus aureus*	2 (22.2)	1 (25)	1 (20)			
Enterobacteriaceae producing ESBL, AmpC BL and carbapenemases	4 (44.4)	2 (50)	2 (40)			
Multidrug-resistant *Pseudomonas aeruginosa*	2 (22.2)	1 (25)	1 (20)			
Other multidrug-resistant microorganisms	1 (11.1)	0	1 (20)			
Clostridioides difficile diarrhea	15 (2.3)	9 (3.04)	6 (1.68)	1.83	0.64-5.21	0.248

Significant *p* values (≤0.05) are highlighted in bold. Abbreviations: CI, confidence interval; OD, odds ratio; SC, Sepsis Code.

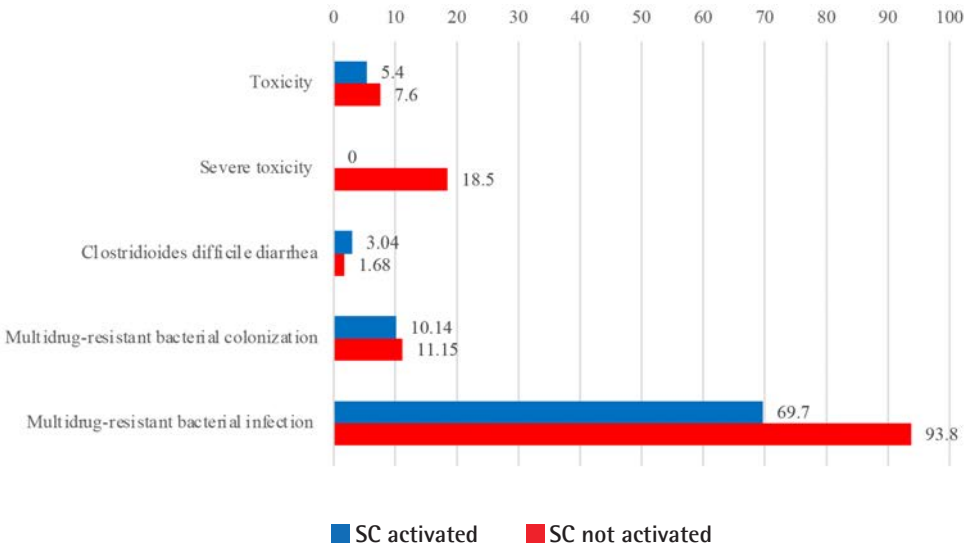


Figure 4 Antibiotic related complications or side effects. Data are expressed as percentages in the two cohorts.

SC: Sepsis Code.

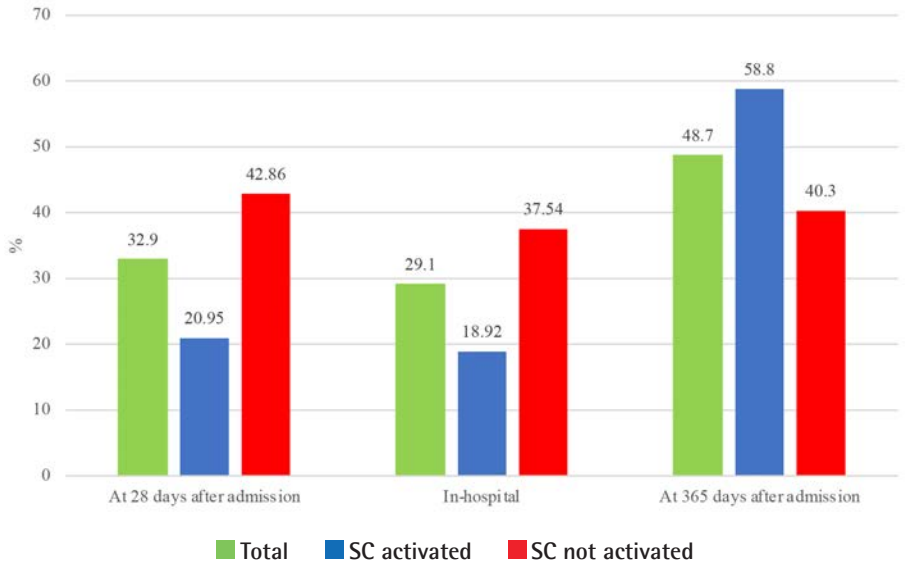


Figure 5 Mortality at different evolution time points according to SC activation. Mortality data are expressed as percentages in the study population and separately in the two cohorts.

range between 12.8 and 26%, which are closer to mortality data in Cohort A than in B. In these series, the lowest mortality values are found in non-severe sepsis; however, our rates do not distinguish groups with different severity of sepsis. Regarding SC, our data show that activation results in a reduction of around a fifty percent in mortality of patients admitted to the IM ward.

The overall mortality rate at one year was 48.7%, sub-

Table 6 Hospital readmissions.

Hospital readmissions	TOTAL	SC activated (A)	SC not activated (B)	OR	CI 95%	p
Hospital readmission within 12 months after discharge, n (%)	154 (32.49)	96 (40)	58 (24.79)	2.02	1.36-2.99	**< 0.001**
Hospital readmission causes, n (%)						
New infection/sepsis	115 (74.7)	70 (72.9)	45 (77.6)	0.77	0.36-1.67	0.519
Heart failure	14 (9.1)	8 (8.3)	8 (10.3)	0.78	0.25-2.39	0.674
Other causes of hospital readmission, n (%)						0.233
Antibiotic toxicity	5 (14.7)	4 (19)	1 (7.7)			
Clostridioides difficile diarrhea	8 (23.5)	3 (14.3)	5 (38.5)			
Others	21 (61.8)	14 (66.7)	7 (53.8)			

Significant *p* values (≤0.05) are highlighted in bold. Abbreviations: CI, confidence interval; OR,odds ratio; SC, Sepsis Code.

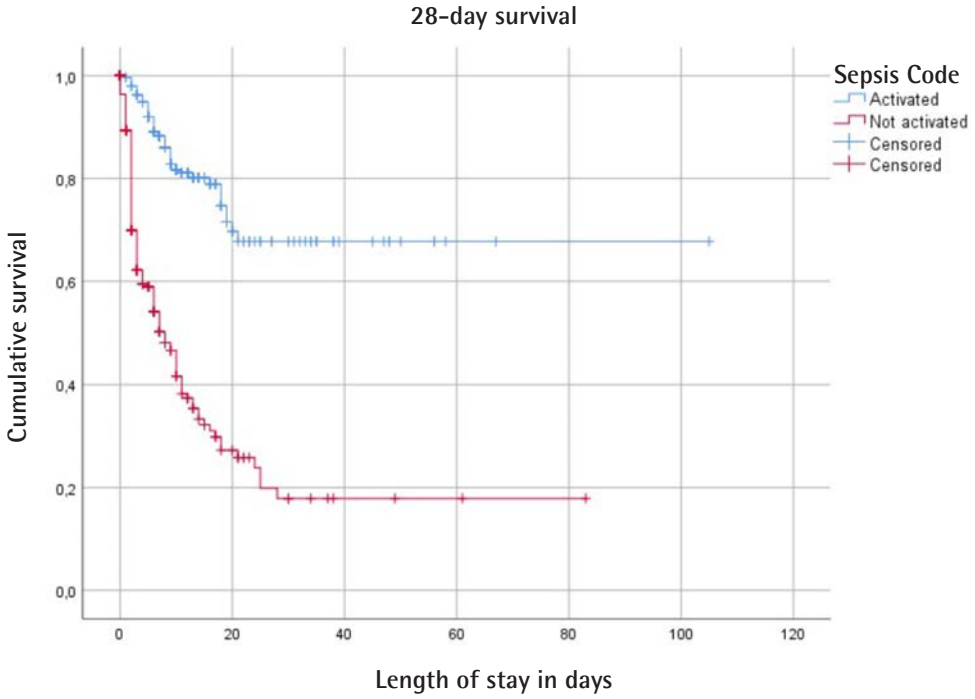


Figure 6 **28-day survival curves according to SC activation. Group A is represented in blue and B in red. Censored refers to patients who survive. The survival rate was higher in the activated SC group (p < 0.001, log-rank test).**

stantially higher than mortality rates reported in previously published studies [30,31,55,56], which range between 21.7 and 31%. This finding is likely to be related to the baseline characteristics of our population: higher mean age and a worse functional status than described series. Furthermore, these baseline conditions are the leading cause of long-term mortality related to sepsis [15,30,32,33,35], regardless of the treatment implemented.

Remarkably, long-term mortality was higher in cohort A than in cohort B. This can be explained by the fact that the baseline characteristics are similar in both cohorts, and the implementation of SC bundles is not enough to combat the severity of morbidity due to sepsis. Female sex, aging, comorbidities, immunosuppression, severity of sepsis and respiratory infections, has been described as independent factors of long-term mortality in several studies [57–59], but these did

not analyze the impact of standard treatment or SC bundles implementation.

Study limitations and strengths. The study has some limitations. It was a retrospective study and the quality of the results therefore depends on correct documentation. No verification of the sepsis diagnostic criteria was performed in group B. Patients were selected in the basis of their discharge diagnosis, and so we may have lost patients in which such term was not properly recorded (codification bias). We did not analyze profoundly readmissions data and so relevant information about evolution could have been lost.

Our study has also several strengths. It includes a large cohort of patients from IM unit and compares two concurrent cohorts considering SC activation.

Conclusions. Patients admitted with a diagnosis of sepsis in IM wards are elderly, with high comorbidity and functional disabilities. This fragility baseline situation is even greater in those patients managed without activating the SC.

More extensive microbiological diagnosis, more intensive treatment and adaptation of antibiotic therapy was performed in SC group. Nevertheless, a longer antibiotic treatment is also administered. This group has better infection control rate at 72 hours, less complications and lower short-term mortality. On the contrary, in-hospital stay, heart failure episode and readmissions increase in patients managed with this protocol.

Implementation of a SCP seems to be effective in improving short-term outcomes of patients admitted in IM units, although therapy should be tailored in an individual basis.

ACKNOWLEDGEMENTS

We would like to acknowledge the contribution of all members of "Sepsis Code Princesa" to the development of the hospital´s programme and its legacy in improving the quality of life of patients.

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1 Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–10. DOI: 10.1097/00003246-200107000-00002.

2 Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland: Crit Care Med 2003;31:2332–8. DOI: 10.1097/01.CCM.0000085141.75513.2B.

3 Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, Hayes SR, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality*: Crit Care Med 2007;35:1105–12. DOI :10.1097/01.CCM.0000259463.33848.3D.

4 Angus DC, Barnato AE, Bell D, Bellomo R, Chong C-R, Coats TJ, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 2015;41:1549–60. DOI: 10.1007/s00134-015-3822-1.

5 Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 2017;376:2235–44. DOI: 10.1056/NEJMoa1703058.

6 Bouza C, López-Cuadrado T, Saz-Parkinson Z, Amate-Blanco JM. Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011). BMC Infect Dis 2014;14:3863. DOI: 10.1186/s12879-014-0717-7.

7 Álvaro-Meca A, Jiménez-Sousa MA, Micheloud D, Sánchez-Lopez A, Heredia-Rodríguez M, Tamayo E, et al. Epidemiological trends of sepsis in the twenty-first century (2000–2013): an analysis of incidence, mortality, and associated costs in Spain. Popul Health Metr 2018;16. DOI: 10.1186/s12963-018-0160-x.

8 Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. Am J Respir Crit Care Med 2017;196:856–63. DOI: 10.1164/rccm.201609-1848OC.

9 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. Crit Care Med 2017;45:486–552. DOI: 10.1097/CCM.0000000000002255.

10 Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the Incidence and Mortality of Severe Sepsis in the United States*: Crit Care Med 2013;41:1167–74. DOI: 10.1097/CCM.0b013e31827c09f8.

11 Palencia Herrejón E, González Del Castillo J, Ramasco Rueda F, Candel FJ, Sánchez Artola B, von Wernitz Teleki A, et al. [Consensus document for sepsis code implementation and development in the Community of Madrid]. Rev Espanola Quimioter Publicacion Of Soc Espanola Quimioter 2019;32:400–9. PMID: 31345006.

12 León Gil C, García-Castrillo Riesgo L, Moya Mir M, Artigas Raventós A, Borges Sa M, Candel González FJ, et al. Documento de Consenso (SEMES-SEMICYUC): Recomendaciones del manejo diagnóstico-terapéutico inicial y multidisciplinario de la sepsis grave en los Servicios de Urgencias hospitalarios. Med Intensiva 2007;31:375–87. DOI: 10.1016/s0210-5691(07)74842-8

13 Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018;44:925–8. DOI: 10.1007/s00134-018-5085-0.

14 Mearelli F, Orso D, Fiotti N, Altamura N, Breglia A, De Nardo M, et al. Sepsis outside intensive care unit: the other side of the coin. Infection 2015;43:1–11. DOI: 10.1007/s15010-014-0673-6.

15 Martin GS, Mannino DM, Moss M. The effect of age on the develop-

ment and outcome of adult sepsis. Crit Care Med 2006;34:15–21. DOI: 10.1097/01.ccm.0000194535.82812.ba.

16 Carmona-Torre F, Martinez-Urbistondo D, Landecho MF, Lucena JF. Surviving sepsis in an intermediate care unit. Lancet Infect Dis 2013;13:294–5. DOI:10.1016/S1473-3099(13)70072-0.

17 Rohde JM, Odden AJ, Bonham C, Kuhn L, Malani PN, Chen LM, et al. The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care unit. J Hosp Med 2013;8:243–7. DOI: 10.1002/jhm.2012.

18 Rhee C, Gohil S, Klompas M. Regulatory Mandates for Sepsis Care — Reasons for Caution. N Engl J Med 2014;370:1673–6. DOI: 10.1056/NEJMp1400276.

19 A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 2014;370:1683–93. DOI: 10.1056/NEJMoa1401602.

20 The PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. N Engl J Med 2017;376:2223–34. DOI: 10.1056/NEJMoa1701380.

21 Hershey TB, Kahn JM. State Sepsis Mandates — A New Era for Regulation of Hospital Quality. N Engl J Med 2017;376:2311–3. DOI: 10.1056/NEJMp1611928.

22 Klompas M, Calandra T, Singer M. Antibiotics for Sepsis—Finding the Equilibrium. JAMA 2018;320:1433. DOI: 0.1001/jama.2018.12179.

23 España, Ministerio de Sanidad SS e I, Boletín Oficial del Estado (España). Clasificacion Internacional de Enfermedades: 10a revisión : Modificación clinica : CIE.10.ES. Vol. 1, Vol. 1,. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad : Boletín Oficial del Estado; 2018.

24 Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288–94. DOI: 10.1016/j.jclinepi.2004.03.012.

25 Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol 2011;173:676–82. DOI: 10.1093/aje/kwq433.

26 Çıldır E, Bulut M, Akalın H, Kocabaş E, Ocakoğlu G, Aydın ŞA. Evaluation of the modified MEDS, MEWS score and Charlson comorbidity index in patients with community acquired sepsis in the emergency department. Intern Emerg Med 2013;8:255–60. DOI: 10.1007/s11739-012-0890-x.

27 Oltean S, Ţăţulescu D, Bondor C, Slavcovici A, Cismaru C, Lupşe M, et al. Charlson's weighted index of comorbidities is useful in assessing the risk of death in septic patients. J Crit Care 2012;27:370–5. DOI: 10.1016/j.jcrc.2011.08.021.

28 Cid-Ruzafa J, Damián-Moreno J. Valoración de la discapacidad física: el indice de Barthel. Rev Esp Salud Pública 1997;71:127–37. DOI: 10.1590/S1135-57271997000200004.

29 Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10:61–3. DOI: 10.3109/09638288809164103.

30 Henriksen DP, Pottegård A, Laursen CB, Jensen TG, Hallas J, Pedersen C, et al. Intermediate-term and long-term mortality among acute medical patients hospitalized with community-acquired sepsis: a population-based study. Eur J Emerg Med 2017;24:404–10. DOI: 10.1097/MEJ.0000000000000379.

31 Schmidt KF, Schwarzkopf D, Baldwin L-M, Brunkhorst FM, Freytag A, Heintze C, et al. Long-Term Courses of Sepsis Survivors: Effects of a Primary Care Management Intervention. Am J Med 2020;133:381-385.e5. DOI: 10.1016/j.amjmed.2019.08.033.

32 Zaccone V, Tosoni A, Passaro G, Vallone CV, Impagnatiello M, Li Puma DD, et al. Sepsis in Internal Medicine wards: current knowledge, uncertainties and new approaches for management optimization. Ann Med 2017;49:582–92. DOI: 10.1080/07853890.2017.1332776.

33 Vardi M, Ghanem-Zoubi NO, Bitterman H, Abo-Helo N, Yurin V, Weber G, et al. Sepsis in nonagenarians admitted to Internal Medicine departments: a comparative study of outcomes. QJM 2013;106:261–6. DOI: 10.1093/qjmed/hcs221.

34 Liu V, Lei X, Prescott HC, Kipnis P, Iwashyna TJ, Escobar GJ. Hospital readmission and healthcare utilization following sepsis in community settings: Healthcare Utilization after Sepsis. J Hosp Med 2014;9:502–7. DOI: 10.1002/jhm.2197.

35 Mazzone A, Dentali F, La Regina M, Foglia E, Gambacorta M, Garagiola E, et al. Clinical Features, Short-Term Mortality, and Prognostic Risk Factors of Septic Patients Admitted to Internal Medicine Units: Results of an Italian Multicenter Prospective Study. Medicine (Baltimore) 2016;95:e2124. DOI: 10.1097/MD.0000000000002124.

36 Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JA, Gordo F, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. Crit Care Med 2007;35:1284–9. DOI: 10.1097/01.CCM.0000260960.94300.DE.

37 Ghanem-Zoubi NO, Vardi M, Laor A, Weber G, Bitterman H. Assessment of disease-severity scoring systems for patients with sepsis in general internal medicine departments. Crit Care Lond Engl 2011;15:R95. DOI: 10.1186/cc10102.

38 Sango A, McCarter YS, Johnson D, Ferreira J, Guzman N, Jankowski CA. Stewardship Approach for Optimizing Antimicrobial Therapy through Use of a Rapid Microarray Assay on Blood Cultures Positive for Enterococcus Species. J Clin Microbiol 2013;51:4008–11. DOI: 10.1128/JCM.01951-13.

39 Campion M, Scully G. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. J Intensive Care Med 2018;33:647–55. DOI: 10.1177/0885066618762747.

40 Tabah A, Cotta MO, Garnacho-Montero J, Schouten J, Roberts JA, Lipman J, et al. A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit. Clin Infect Dis 2016;62:1009–17. DOI: 10.1093/cid/civ1199.

41 Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis 2012;12:919–24. DOI: 10.1016/S1473-3099(12)70239-6.

42 Stiermaier T, Herkner H, Tobudic S, Burgmann K, Staudinger T, Schellongowski P, et al. Incidence and long-term outcome of sepsis on general wards and in an ICU at the General Hospital

of Vienna: an observational cohort study. Wien Klin Wochenschr 2013;125:302–8. DOI: 10.1007/s00508-013-0351-1.

43 Pinilla Rello A, Huarte Lacunza R, Magallón Martínez A, Marrón Tundidor R, Martínez Álvarez R, Bustamante Rodríguez E, et al. Evaluación de los resultados de la implantación del Código Sepsis en el servicio de urgencias de un hospital terciario. J Healthc Qual Res 2020;35:281–90. DOI: 10.1016/j.jhqr.2020.06.008.

44 García-López L, Grau-Cerrato S, de Frutos-Soto A, Bobillo-De Lamo F, Cítores-Gónzalez R, Diez-Gutierrez F, et al. Impact of the implementation of a Sepsis Code hospital protocol in antibiotic prescription and clinical outcomes in an intensive care unit. Med Intensiva Engl Ed 2017;41:12–20. DOI: 10.1016/j.medine.2017.02.001.

45 De Waele JJ, Schouten J, Beovic B, Tabah A, Leone M. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions—a viewpoint of experts. Intensive Care Med 2020;46:236–44. DOI: 10.1007/s00134-019-05871-z.

46 Seok H, Jeon JH, Park DW. Antimicrobial Therapy and Antimicrobial Stewardship in Sepsis. Infect Chemother 2020;52:19–30. DOI: 10.3947/ic.2020.52.1.19.

47 Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 2014;40:32–40. DOI: 10.1007/s00134-013-3077-7.

48 Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018;18:95–107. DOI: 10.1016/S1473-3099(17)30592-3.

49 Hranjec T, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet Infect Dis 2012;12:774–80. DOI: 10.1016/S1473-3099(12)70151-2.

50 Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*: Crit Care Med 2006;34:1589–96. DOI: 10.1097/01.CCM.0000217961.75225.E9.

51 Gutiérrez Junco SM, Paipa Merchán AJ, Heredia Rodríguez M, Gómez Herreras JI, Tamayo Gómez E. The Resuscitation Bundle of the Surviving Sepsis Campaign Beyond Early Goal-Directed Therapy: What's Next? Crit Care Med 2015;43:e319-320. DOI: 10.1097/CCM.0000000000000960.

52 Goodwin AJ, Rice DA, Simpson KN, Ford DW. Frequency, Cost and Risk Factors of Readmissions among Severe Sepsis Survivors. Crit Care Med 2015;43:738–46. DOI: 10.1097/CCM.0000000000000859.

53 Prescott HC, Langa KM, Iwashyna TJ. Readmission Diagnoses After Hospitalization for Severe Sepsis and Other Acute Medical Conditions. JAMA 2015;313:1055. DOI: 0.1001/jama.2015.1410.

54 Shankar-Hari M, Saha R, Wilson J, Prescott HC, Harrison D, Rowan K, et al. Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. Intensive Care Med 2020;46:619–36. DOI: 10.1007/s00134-019-05908-3.

55 Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, Shah NH, et al. The impact of acute organ dysfunction on long-term survival among sepsis survivors. Crit Care Med 2018;46:843–9. DOI: 10.1097/CCM.0000000000003023.

56 Storgaard M, Hallas J, Gahrn-Hansen B, Pedersen SS, Pedersen C, Lassen AT. Short- and long-term mortality in patients with community-acquired severe sepsis and septic shock. Scand J Infect Dis 2013;45:577–83. DOI: 10.3109/00365548.2013.786836.

57 Courtright KR, Jordan L, Murtaugh CM, Barrón Y, Deb P, Moore S, et al. Risk Factors for Long-term Mortality and Patterns of End-of-Life Care Among Medicare Sepsis Survivors Discharged to Home Health Care. JAMA Netw Open 2020;3. DOI: 10.1001/jamanetworkopen.2020.0038.

58 Francisco J, Aragão I, Cardoso T. Risk factors for long-term mortality in patients admitted with severe infection. BMC Infect Dis 2018;18. DOI: 10.1186/s12879-018-3054-4.

59 Linnér A, Sundén-Cullberg J, Johansson L, Hjelmqvist H, Norrby-Teglund A, Treutiger CJ. Short- and Long-Term Mortality in Severe Sepsis/Septic Shock in a Setting with Low Antibiotic Resistance: A Prospective Observational Study in a Swedish University Hospital. Front Public Health 2013;1. DOI: 10.3389/fpubh.2013.00051.

Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/150.2021

Ferrán Llopis-Roca[1]
Raúl López Izquierdo[2]
Oscar Miro[3]
Jorge Eric García-Lamberechts[4]
Agustín Julián Jiménez[5]
Juan González del Castillo[6]

Mapa de la situación actual de la atención a la sepsis en los servicios de urgencias españoles

[1]Servicio de Urgencias, Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat, Barcelona, España
[2]Servicio de Urgencias, Hospital Universitario Rio Hortega, Valladolid, España
[3]Servicio de Urgencias, Hospital Clinic de Barcelona, España
[4]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, España
[5]Servicio de Urgencias, Complejo Hospitalario de Toledo, España
[6]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, España
Facultad de Medicina, Universidad Complutense de Madrid, España

Article history
Received: 18 October 2021; Revision Requested: 26 November 2021; Revision Received: 28 November 2021; Accepted:10 December 2021; Published: 1 February 2022

RESUMEN

Objetivo. Describir el abordaje que se realiza a los pacientes con sospecha de sepsis en los servicios de urgencias hospitalarios (SUH) españoles y analizar si existen diferencias atendiendo al tamaño del hospital y la afluencia a urgencias en el territorio.

Método. Encuesta estructurada a los responsables de los 282 SUH públicos que atienden adultos 24 horas/día, 365 días/año. Se preguntó sobre asistencia y manejo en urgencias en la atención a pacientes con sospecha de sepsis. Los resultados se comparan según tamaño del hospital (grande ≥ 500 camas vs medio-pequeño < 500) y afluencia en urgencias (alta ≥ 200 visitas/día vs media-baja < 200).

Resultados. Respondieron 250 SUH españoles (89%). En 163 (65%) SUH se dispone de protocolos de sepsis. La mediana de sepsis semanales atendidas variaban desde 0-5 por semana en 39 (71%) SUH, 6-10 por semana en 10 (18%), 11-15 por semana en 4 (7%), y más de 15 activaciones por semana en 3 centros (3,6%). Los criterios utilizados para la activación del código sepsis (CS) fueron el qSOFA/SOFA en 105 (63,6%) de los hospitales, SIRS en 6 (3,6%), mientras que en 49 (29,7%) utilizaban ambos criterios de forma simultanea. En 79 centros el CS estaba informatizado y en 56 existían herramientas de ayuda a la toma de decisiones. Un 48% (79 de 163) de los SUH disponían de datos de cumplimiento de medidas. En el 61% (99 de 163) de SUH existía formación en sepsis y en el 56% (55 de 99) ésta era periódica. Atendiendo al tamaño del hospital, los hospitales grandes participaban más frecuentemente como receptores de enfermos con CS y disponían de servicio/unidad de infecciosas, de sepsis y de corta estancia, microbiólogo e infectólogo de guardia.

Conclusión. la mayoría de los SUH disponen de protocolos de CS, pero existe margen de mejora. La informatización y desarrollo de alertas para el diagnóstico y tratamiento tienen aún un gran recorrido en los SUH.

Palabras clave: sepsis, código sepsis, urgencias

Current situation of sepsis care in Spanish emergency departments

ABSTRACT

Objective. To describe the approach to the patients with suspected sepsis in the Spanish emergency department hospitals (ED) and analyze whether there are differences according to the size of the hospital and the number of visits to the emergency room.

Method. Structured survey of those responsible for the 282 public EDs that serve adults 24 hours a day, 365 days a year. It was asked about assistance and management in the emergency room in the care of patients with suspected sepsis. The results are compared according to hospital size (large ≥ 500 beds vs medium-small <500) and influx to the emergency room (discharge ≥ 200 visits / day vs medium-low <200).

Results. A total of 250 Spanish EDs responded (89%). Sepsis protocols are available in 163 (65%) EDs median weekly sepsis treated ranged from 0-5 per week in 39 (71%) ED, 6-10 per week in 10 (18%), 11-15 per week in 4 (7%), and more than 15 activations per week in 3 centers (3.6%). The criteria used for sepsis diagnosis were the qSOFA/SOFA in 105 (63.6%) of the hospitals, SIRS in 6 (3.6%), while in 49 (29.7%) they used both criteria simultaneously. In 79 centers, the sepsis diagnosis was computerized, and in 56 there were tools to help decision-making. 48% (79 of 163) of the EDs had data on bundles compliance. In 61% (99 of 163) of EDs there was training in sepsis and in 56% (55 of 99) it was periodic. Considering the size of the hospital, large hospitals participated

Correspondencia:
Juan González del Castillo
Servicio de Urgencias
Hospital Clínico San Carlos
Calle Profesor Martín Lagos s/n. Madrid 28040
Tlf. 913303750 - Fax. 913303569
E-mail: jgonzalezcast@gmail.com

more frequently as recipients of patients with sepsis and had an infectious, sepsis and short-stay unit, a microbiologist and infectious disease specialist on duty.

Conclusion. Most EDs have sepsis protocols, but there is room for improvement. The computerization and development of alerts for diagnosis and treatment still have a long way to go in EDs.

Key words: Sepsis, sepsis code, emergency departments

INTRODUCCIÓN

La incidencia de la infección en los servicios de urgencias hospitalarios (SUH) suponía el 14,3% de las visitas diarias hace una década [1], aunque se estima que esta ha podido aumentar en los últimos años [2]. Por otra parte, la incidencia y la prevalencia de la sepsis no resulta tan clara de conocer, ya que ambas varían en función de las definiciones utilizadas, las cuales han ido cambiando en el devenir de los años. Esto da lugar a que puede registrarse una incidencia del 6,2% del total de las infecciones diagnosticadas, si se utilizan los criterios clásicos de sospecha de infección y síndrome de respuesta inflamatoria sistémica (SIRS) [1], o del 30% si se tienen en cuenta otras definiciones o criterios [3,4].

Se sabe que la sepsis es una de las enfermedades denominadas tiempo-dependientes, en las cuales es de suma importancia su detección precoz para poder establecer el tratamiento lo más rápido posible, ya que la demora en su inicio y mantenimiento se asocia a un aumento de la morbilidad y mortalidad en los pacientes que la sufren [5]. Desde la publicación de las últimas definiciones de la sepsis en el año 2016 [6,7] se han establecido métodos diagnósticos de cara a identificar precozmente al paciente séptico basados en el uso de diferentes escalas de gravedad como el Quick Sequential Organ Failure Assessment (qSOFA), el National Early Warning Score (NEWS) o el Sequential Organ Failure Assessment (SOFA) y la determinación de biomarcadores como el ácido láctico, la proteína C reactiva (PCR) o la procalcitonina (PCT). Aún hoy sigue abierto el debate científico sobre cuáles son los mejores criterios para identificar el paciente con sepsis en los servicios de urgencias [8].

En esta línea, ya hace unos años se creó el concepto de código sepsis (CS), cuyo objetivo último es facilitar la detección de los enfermos con sospecha de sepsis en cualquier nivel asistencial, e intentar estandarizar el cumplimiento de toda una serie de medidas terapéuticas desde el minuto cero y durante las primeras horas tras su detección, y todo ello con equipos multidisciplinares, con la implicación de diferentes especialidades médicas, quirúrgicas y de enfermería.

A pesar de todo esto la sepsis sigue teniendo cifras inaceptables de mortalidad llegando en el caso del shock séptico al 15-50% [3], siendo aún una patología infradiagnosticada en todos los ámbitos sanitarios. En los SUH se cree que pueden pasar inadvertidos casi el 50% de los pacientes sépticos [4].

Aún hoy, se desconoce el grado de implantación del CS en el ámbito hospitalario de nuestro país, así como la disponibilidad de los diferentes biomarcadores de infección o el uso que se hacen de las escalas diagnósticas. Es por ello que se diseñó el presente estudio, cuyo objetivo principal fue conocer el abordaje que se realiza actualmente a los pacientes con sospecha de sepsis en los SUH españoles, y averiguar si existen diferencias en función del tamaño del hospital y de la afluencia de pacientes que recibe dicho SUH.

MÉTODO

Este estudio se basa en una encuesta de opinión en la que se recogieron, por una parte, datos genéricos de los hospitales y de sus SUH (población de referencia, número de camas de hospitalización, existencia de unidad/servicio de infecciosas y microbiólogo e infectólogo de guardia de presencia física todo el año y número de atenciones diarias) y, por otra parte, datos específicos de la atención practicada a los pacientes que consultaron por sospecha de sepsis en los SUH (Material suplementario – Anexo 1). La encuesta se diseñó entre septiembre y octubre de 2020, y para evitar el efecto de la pandemia COVID-19 en la actividad asistencial, se solicitaron los datos del año 2019 [9,10].

El universo a estudio fue todos los SUH del sistema público de salud español que atienden urgencias generales de pacientes adultos, 24 horas al día, 7 días a la semana y los 365 días (24/7/365) en el año 2019. El estudio se diseñó en base a una intención de inclusión total, con el objetivo de obtener un mapa de la atención a la sepsis en los SUH de nuestro país. La fuente de centros la constituyó el Catálogo Nacional de Hospitales de 2019 [11] con 924 centros. Se excluyeron 642 (323 por no ser generales, 315 privados sin concierto, 2 militares y 2 cerrados el 2019), por lo que el universo a encuestar fue de 282 SUH.

La encuesta se remitió al responsable del SUH, con quien previamente se había contactado por teléfono para explicarle el proyecto y solicitar su colaboración. Se envió telemáticamente un enlace a la encuesta en línea para poder completarla y también en formato *pdf* por correo electrónico por si prefería escanearla y enviar las respuestas por e-mail. Si después de 3 contactos no se recibía respuesta se consideraba ese SUH como no respondedor. Las entrevistas se realizaron durante diciembre de 2020 y enero y febrero de 2021.

Análisis estadístico. Los datos continuos se presentan como mediana y rango intercuartil (RIC), y los discretos como valores absolutos y porcentajes. Los centros se agruparon en función del número de camas (grandes ≥ 500; medios/pequeños < 500) y de la afluencia de pacientes (alta ≥ 200/día; media/baja < 200) siguiendo la definición de trabajos previos [12]. La comparación entre los grupos se realizó mediante el test no paramétrico de Mann-Whitney si las variables eran continuas y mediante el test de ji cuadrado si las variables eran discretas. Un valor de $p < 0,05$ se consideró estadísticamente significativo.

Consideraciones éticas. Por las características del estudio, éste no fue valorado por ningún Comité Ético en Inves-

tigación Clínica. Se garantizó la confidencialidad de los datos individuales y se solicitó su aprobación verbal para participar voluntariamente en el estudio.

RESULTADOS

De los 282 responsables de los SUH contactados respondieron 250 (89%), con una tasa de respuesta superior al 80% en las Ciudades Autónomas de Ceuta, Melilla y en 14 de las 17 Comunidades Autónomas (Tabla 1). De los 250 SUH, 59 (24%) correspondían a hospitales grandes y 114 (46%) reportaban una actividad asistencial alta, con una población total asignada de 19,5 millones los hospitales grandes (mediana: 0,35, RIC: 0,30-0,46) y 26,2 millones los hospitales medianos/pequeños (mediana: 0,13, RIC: 0,06-0,19). En el año 2019 los 250 SUH analizados realizaron 19,4 millones de asistencias (mediana: 0,07, RIC: 0,03-0,11).

El 46% de los SUH disponían de servicio o unidad de infecciosas de hospitalización y el 33% y el 5% contaban, respectivamente, con microbiólogo e infectólogo de guardia 24/7/365. Solamente 21 SUH (8%) respondieron disponer de unidad de sepsis. Sin embargo, 99 de 249 (40%) eran receptores de enfermos con CS, 163 (65%) disponían de protocolos de sepsis urgente y 114 (46%) de hospitalización. La mediana de sepsis semanales atendidas en estos SUH fue muy variable, 55 de 165 (33%) SUH respondieron conocer el número de activaciones semanales, que variaban desde 0-5 por semana en 39 (71%) SUH, 6-10 por semana en 10 (18%), 11-15 por semana en 4 (7%), a hasta más de 15 activaciones por semana en 3 centros (3,6%). Al preguntar por las falsas activaciones, 31 de estos 55 (56%) SUH respondieron no tener ninguna, 15 (27%) un porcentaje de falsas activaciones inferior al 10% y 9 (16%) de más del 11%, estos últimos correspondían mayoritariamente a los centros que más CS activaban.

En la mayoría de los casos (58%) el CS lo podía activar medicina o enfermería. Los criterios utilizados para la activación del CS fueron el qSOFA/SOFA en 105 (64%) de los hospitales, SIRS en 6 (3,6%), mientras que en 49 (30%) utilizaban ambos criterios de forma simultanea. Cinco (3%) centros manifestaron seguir criterios propios. En 79 centros el CS estaba informatizado y en 56 existen herramientas de ayuda a la toma de decisiones como calculadoras de escalas, sistemas de alerta o guías para el uso de antimicrobianos.

Un 48% (79 de 163) de los SUH disponían de datos de cumplimiento de medidas: toma de lactato en el 97%, hemocultivos y fluidoterapia en el 99% y antibioterapia precoz en el 100%. En 159 de 163 (98%) de los hospitales se utilizaban biomarcadores, siendo el lactato y la PCR los que se usaban mayoritariamente de forma rutinaria. En el 61% (99 de 163) de SUH existía formación en sepsis y en el 56% (55 de 99) ésta era periódica. Las características asistenciales de los pacientes con sospecha de sepsis en los SUH españoles se recogen en la Tabla 2.

Al comparar el manejo de la sepsis en los SUH atendiendo al tamaño del hospital, observamos que los hospitales grandes (≥ 500 camas) respecto los medianos/pequeños (< 500) participaban más frecuentemente como receptores de enfermos con CS activado pre-hospitalario e intrahospitalario y disponían de servicio/unidad de infecciosas, de sepsis y de corta estancia, microbiólogo e infectólogo de guardia 7/24/365 de forma estadísticamente significativa ($p < 0,05$). El resto de elementos comparados se observan en la Tabla 3.

Tabla 1 **Distribución geográfica de los Servicios de Urgencias Hospitalarios (SUH) españoles que contestaron la encuesta.**

	SUH públicos existentes (N)	SUH públicos participantes (N)	Participación (%)
Catalunya	54	50	93
Andalucía	53	44	83
Comunidad Valenciana	26	25	96
Comunidad de Madrid	25	25	100
Galicia	16	14	87,5
Castilla y León	15	14	93
Castilla-La Mancha	14	12	86
Canarias	13	11	85
País Vasco	12	10	83
Aragón	10	9	90
Principado de Asturias	9	9	100
Región de Murcia	9	8	89
Extremadura	8	5	62,5
Illes Balears	7	4	57
Cantabria	4	4	100
Comunidad Foral de Navarra	3	2	67
La Rioja	2	2	100
Ciudades Autónomas de Ceuta y Melilla	2	2	100
Total	282	250	89

La Tabla 4 muestra los resultados que se obtienen al comparar los SUH en función de la afluencia de pacientes, ya sea esta alta (≥ 200 visitas/día) o media/baja (< 200).

En las Figuras 1 y 2 se representa la implementación del CS en las diferentes Comunidades Autónomas.

DISCUSIÓN

El CS se ha ido instaurando estos últimos años de forma progresiva con diferentes iniciativas que han permitido el desarrollo de distintos protocolos, lo que ha podido ayudar a su implantación en los SUH [13-15]. Se ha descrito alguna estimación que fijaba la implantación del CS entre los SUH españoles en alrededor del 30-50% [4]. Sin embargo, de nuestro

Tabla 2 **Características asistenciales a los pacientes con sospecha de sepsis en los SUH españoles.**

PREGUNTA	SÍ	NO	(%)
¿Existe Servicio/Unidad de infecciosas?	114	135	46
¿Existe Microbiólogo 24/7/365?	83	166	33
¿Existe Infectólogo 24/7/365?	12	237	5
¿Existe Unidad de sepsis?	21	228	8
¿Es receptor de enfermos con código sepsis (CS)?	99	150	40
¿Dispone de protocolo de sepsis urgente?	163	87	65
¿Dispone de protocolo de sepsis de hospitalización?	114	136	46
¿Se diagnostican menos sepsis desde el COVID?	96	74	56
¿Está informatizado el CS?	79	89	47
¿Dispone de herramientas de ayuda de decisión?	56	25	69
Calculadora de escalas	47	9	84
Sistemas de alerta	42	14	75
Antibioterapia	34	22	61
¿Tiene acceso a los criterios de activación del CS?	55	110	33
¿Datos de cumplimiento de medidas?	79	84	48
Lactato	77	2	97
Hemocultivos	78	1	99
Antibioticoterapia precoz	79	0	100
Fluidoterapia	78	1	99
Control del foco	71	8	90
¿Uso de biomarcadores?	159	4	98
¿Existe formación en sepsis?	99	64	61
¿La formación es periódica?	55	44	56
¿Existe mejora del manejo de la sepsis con el código?	156	7	96
¿El Servicio de Urgencias forma parte del equipo de sepsis intrahospitalaria?	96	19	83
PREGUNTA			N (%)
¿Quién activa el CS? (n=166)			
Médico adjunto			27 (16)
Cualquier medico			39 (23)
Enfermería			3 (1,8)
Médico/enfermería			97 (58)
Criterios de activación del CS (n=165)			
SIRS			6 (3,6)
qSOFA/SOFA			105 (64)
Ambos			49 (30)
Propios			5 (3)
¿Se cumplen todos las bundles de las primera hora? (n=19)			
Desconoce			2 (10,5)
<25%			4 (21)
26-50%			1 (5)
51-75%			8 (42)
76-100%			4 (21)

Tabla 2 **Características asistenciales a los pacientes con sospecha de sepsis en los SUH españoles (cont.)**

PREGUNTA	N (%)
Biomarcadores (n=159)	
Lactato	
No disponible en urgencias	3 (1,9)
Disponible, pero no se usa nunca o casi nunca	0 (0,0)
Disponible, se usa en algunos casos (<25%)	4 (2,5)
Disponible, se usa en bastantes casos (25%-75%)	14 (9)
Disponible, se usa de forma rutinaria (>75%)	138 (87)
PCR	
No disponible en urgencias	2 (1,3)
Disponible, pero no se usa nunca o casi nunca	1 (0,6)
Disponible, se usa en algunos casos (<25%)	3 (1,9)
Disponible, se usa en bastantes casos (25%-75%)	10 (6)
Disponible, se usa de forma rutinaria (>75%)	143 (90)
Procalcitonina	
No disponible en urgencias	17 (11)
Disponible, pero no se usa nunca o casi nunca	2 (1,3)
Disponible, se usa en algunos casos (<25%)	9 (6)
Disponible, se usa en bastantes casos (25%-75%)	22 (14)
Disponible, se usa de forma rutinaria (>75%)	109 (69)
Coordinador de la sepsis intrahospitalaria (n=114)	
Medicina interna	22 (19)
Urgencias	21 (18)
Medicina intensiva	50 (44)
Enfermedades infecciosas	14 (12)
Otro	7 (6)

trabajo se desprende que la implantación de este código supera ampliamente el 50% de los SUH de hospitales analizados, situándose con los datos proporcionados por sus responsables en el 65%, lo que confirma la preocupación por este problema entre los médicos de urgencias de nuestro país, si bien hay diferencias entre las diferentes Comunidades Autónomas. Creemos, no obstante, que se necesitaría un impulso mayor para que este protocolo se extendiera a más hospitales, ya que según los datos actuales 2 de cada 3 sepsis que se diagnostican en los hospitales son valorados en los SUH [16-18] y entre el 50-60% de los pacientes sépticos o con shock séptico que ingresan en las unidades de críticos proceden del SUH [4].

Nuestros hallazgos ponen de relieve que el CS está más desarrollado en los SUH que en otros niveles asistenciales como la atención pre-hospitalaria o en propio ámbito hospitalario, en el que no llegan al 50% de los casos según lo manifestado por los encuestados. Esto contrasta con el desarrollo alcanzado en los últimos años de otros códigos de patologías tiempo dependientes, como el código infarto o el código ictus, en los que el avance de las técnicas intervencionistas y la mejora en la coordinación entre los diferentes niveles asistenciales [19,20] ha hecho que estos códigos se establezcan de forma rutinaria y sean una prioridad en todos los sistemas de salud de nuestro país [21]. Tal vez el hecho de que el CS sea un proceso con una gran heterogeneidad y la falta aún de una prueba diagnóstica estándar [22], unido a que no exista una técnica terapéutica tan efectiva como la reperfusión del tejido cardiaco o cerebral que desarrollan especialidades muy específicas, haya generado un retraso en su desarrollo global. En todo caso, pensamos que desde los servicios de urgencias, al ser el primer eslabón en la cadena asistencial de estos pacientes, se tendría que impulsar medidas para el avance global del CS y liderar desde nuestro ámbito sanitario estas iniciativas [4]. No obstante, dado el carácter transversal de esta patología es fundamental e imprescindi-

Tabla 3 **Comparación del manejo de la sepsis en función del tamaño del hospital.**

	≥ 500 camas N=59 (%)	< 500 camas N=191 (%)	P
Servicio de infecciosas	53/59 (90)	61/190 (32)	<0,001
Microbiólogo de guardia 24/7/365	41/59 (69)	42/190 (22)	<0,001
Infectólogo de guardia 24/7/365	9/59 (15)	3/190 (1,5)	<0,001
Unidad de Corta Estancia	30/59 (51)	58/190 (31)	0,004
Unidad de sepsis	11/59 (19)	10/190 (5)	0,001
Participación CS: receptor de enfermos con CS activado pre-hospitalario	33/59 (56)	66/190 (35)	0,004
Participación CS: protocolo CS en Urgencias (UCIAS)	43/59 (73)	120/191 (63)	0,156
Participación CS intrahospitalario (no incluye el de UCIAS)	39/59 (66)	75/191 (39)	<0,001
Desde la aparición de la COVID, ¿se diagnostican menos sepsis en urgencias?	26/44 (59)	70/126 (56)	0,684
¿El CS está informatizado?	22/44 (50)	57/124 (46)	0,645
Si el CS está informatizado, ¿existen herramientas de ayuda a la decisión?	17/22 (77)	39/57 (68)	0,604
Calculadora de escalas	12/17 (71)	35/39 (90)	0,073
Sistemas de alerta	11/17 (65)	31/39 (79)	0,240
Desplegables/pautas antibiótico	12/17 (71)	22/39 (56)	0,318
¿Quién puede activar el CS?			0,177
Médico adjunto	4/43 (9)	23/123 (19)	
Cualquier médico	9/43 (21)	30/123 (24)	
Enfermería	2/43 (4,65)	1/123 (0,81)	
Médico/enfermería	28/43 (65)	69/123 (56)	
Criterios de activación CS en urgencias			0,486
SRIS (previos)	1/43 (2,33)	5/122 (4,98)	
qSOFA/SOFA (nuevos)	24/43 (56)	81/122 (66)	
SRIS/qSOFA/SOFA	16/43 (37)	33/122 (27)	
Propios	2/43 (4,65)	3/122 (2,46)	
¿Tiene acceso a datos de activación?	12/43 (28)	43/122 (35)	0,380
Número semanal de activaciones	12	43	<0,001
0-5	2	37	
6-10	7	3	
> 11	3	3	
Datos de falsas activaciones	12	43	0,110
No	7	24	
0-10%	1	14	
> 11%	4	5	
¿Se recogen datos del cumplimiento de los paquetes de medidas?	28/43 (65)	51/120 (42,5)	0,011
Lactato	28/28 (100)	49/51 (96)	0,289
Hemocultivos	28/28 (100)	50/51 (98)	0,456
Antibiótico precoz	28/28 (100)	51/51 (100)	1.000
Infusión intensiva de sueros	28/28 (100)	59/51 (98)	0,456
Control temprano del foco infeccioso	27/28 (97)	44/51 (86)	0,152

Tabla 3 **Comparación del manejo de la sepsis en función del tamaño del hospital (cont.)**

	≥ 500 camas N=59 (%)	< 500 camas N=191 (%)	P
Uso de biomarcadores en Urgencias	43/43 (100)	116/120 (97)	0,225
¿Existe formación en sepsis?	29/43 (67)	70/120 (58)	0,294
¿La formación es periódica?	18/29 (62)	37/70 (53)	0,401
¿Ha mejorado el manejo de la sepsis desde la implantación del CS?	40/43 (93)	116/120 (97)	0,312
¿El servicio de UCIAS forma parte del equipo/estructura del CS intrahospitalario?	34/39 (87)	62/76 (82)	0,444
¿Quién coordina el CS intrahospitalario?			0,039
Medicina interna	2/39 (5)	20/75 (27)	
Urgencias	6/39 (15)	15/75 (20)	
Medicina intensiva	23/39 (59)	27/75 (36)	
Enfermedades infecciosas	6/39 (15)	8/75 (11)	
Otro	2/39 (5)	5/75 (7)	

ble la implicación de diferentes especialidades involucradas en el manejo de estos pacientes.

Se ha observado que los hospitales de mayor tamaño y que realizan más atenciones parecen tener una actitud más proactiva en el abordaje integral de los pacientes con sospecha de sepsis a tenor de los resultados obtenidos, hallazgo por otra parte esperable ya que disponen de más recursos, lo que comporta poder desarrollar más o mejores estrategias. Sin embargo, creemos que algunas de las implementaciones pueden resultar lo suficientemente simples como para que sean adoptadas en cualquier SUH, independientemente del tamaño del centro o de su afluencia en Urgencias. Más aún teniendo en cuenta que los hospitales de tamaño más pequeño dan soporte a más de la mitad de la población española, por lo que no deberían ser excluidos de cualquier actuación frente una enfermedad tiempo-dependiente como la sepsis.

Por otra parte, con la disponibilidad de las nuevas tecnologías, creemos que la informatización del CS resulta de especial interés. Sin embargo, solo el 47% de SUH respondieron disponer de un CS informatizado. En este sentido, disponer de herramientas de ayuda en la decisión como las calculadoras de escalas, sistemas de alerta o de antibioterapia han demostrado resultados muy favorables. En un estudio de Ferreras et al. en Aragón [23], la implementación de un sistema de alarmas automático para la detección precoz de los pacientes con sepsis grave obtuvo una reducción de mortalidad en términos absolutos del 11,3% al ingreso y una mayor supervivencia a los 30 días de forma significativa, siendo el NNT de 8. Los autores concluyeron que la ausencia de sistemas de detección automática en urgencias implicaba un riesgo 2,02 veces mayor de muerte a los 30 días que si se disponía de este sistema.

De forma paralela a esta baja informatización de los sistemas, se observa el pequeño número de hospitales que recogen los datos de cumplimiento de las medidas básicas iniciales ante la sospecha de un paciente con sepsis, lo que impide en gran medida tener una monitorización de las actuaciones que se están llevando a cabo, algo básico para detectar áreas de mejora y reconocer aquellas que se muestren realmente eficaces en el manejo de los pacientes [14,15,20].

Uno de los puntos clave en la actuación en los pacientes con sepsis es el reconocimiento precoz en los servicios de urgencias y emergencias. En esta línea, en los últimos años se han propuesto diferentes escalas para su identificación. Actualmente la gran mayoría de los hospitales que tienen un CS en el SUH detectan los pacientes sépticos mediante las escalas SOFA o qSOFA, que podríamos catalogarlos como los estándares actuales para la valoración del deterioro de la función de órganos entre los pacientes con sospecha de infección. El uso de estas escalas ha aumentado de forma muy importante, ya que su uso exclusivo ha pasado de un 25% a un 63%, mientras que el uso combinado de estas dos escalas junto con el SIRS ha bajado del 50% al 30% en los últimos años [4]. Parece claro que, a pesar de las limitaciones de estas escalas en términos de sensibilidad y especificidad para la valoración del paciente séptico en los SUH [24,25], su implantación actual en los SUH españoles es indudable.

Otro punto crítico es el uso de los biomarcadores que se recomiendan para la valoración inicial de los pacientes sépticos. Es llamativo que el ácido láctico no esté disponible en el 100% de los hospitales consultados y no se use de forma rutinaria en el 13,2% de los SUH. En nuestra opinión, se debe promover y favorecer el uso del ácido láctico, que juega un papel fundamental en la valoración pronóstica de los pacientes sépticos. Diferentes estudios muestran que es un marcador independiente de mortalidad entre los pacientes sépticos [26,27], además de ser en la actualidad uno de los parámetros

Tabla 4 **Comparación del manejo de la sepsis en función de la afluencia a los SUH.**

	≥ 200 visitas/día N=111 (%)	< 200 visitas/día N=136 (%)	P
Servicio de infecciosas	85/111 (77)	27/135 (20)	<0,001
Microbiólogo de guardia 24/7/365	54/111 (49)	27/135 (20)	<0,001
Infectólogo de guardia 24/7/365	10/111 (9)	2/135 (1,48)	0,006
Unidad de Corta Estancia	47/111 (42)	40/135 (30)	0,038
Unidad de sepsis	14/111 (13)	6/135 (4,44)	0,020
Participación CS: receptor de enfermos con CS activado pre-hospitalario	61/111 (55)	37/135 (27)	<0,001
Participación CS: protocolo CS en Urgencias (UCIAS)	86/111 (77)	74/136 (54)	<0,001
Participación CS intrahospitalario (no incluye el de UCIAS)	72/111 (65)	39/136 (29)	<0,001
Desde la aparición de la COVID, ¿se diagnostican menos sepsis en UCIAS?	55/88 (62,5)	40/79 (51)	0,122
¿El CS está informatizado?	46/87 (53)	31/78 (40)	0,091
Si el CS está informatizado, ¿existen herramientas de ayuda a la decisión?	35/46 (76)	19/31 (61)	0,241
Calculadoras de escalas	27/35 (77)	19/20 (95)	0,085
Sistemas de alerta	25/35 (71)	16/20 (80)	0,483
Desplegables/pautas antibiótico	20/35 (57)	13/20 (65)	0,567
¿Quién puede activar el CS?			0,043
Médico adjunto	8/86 (9)	19/77 (25)	
Cualquier médico	19/86 (22)	19/77 (25)	
Enfermería	2/86 (2,33)	1/77 (1,29)	
Médico/enfermería	57/86 (66)	38/77 (49)	
Criterios de activación CS UCIAS			0,487
SRIS (previos)	1/86 (2,33)	4/76 (5)	
qSOFA/SOFA (nuevos)	57/86 (55,81)	47/76 (62)	
SRIS/qSOFA/SOFA	25/86 (37,21)	23/76 (30)	
Propios	3/86 (4,65)	2/76 (2,63)	
¿Tiene acceso a datos de activación?	27/86 (31)	27/76 (36)	0,578
Número semanal de activaciones	27	27	0,011
0-5	15	24	
6-10	9	0	
> 11	3	3	
Datos de falsas activaciones	27	27	0,222
No	19	12	
0-10%	5	10	
> 11%	3	5	
¿Se recogen datos del cumplimiento de los pauetes de medidas?	50/86 (58)	27/74 (36)	0,006
Lactato	49/50 (98)	26/27 (96)	0,654
Hemocultivos	50/50 (100)	26/27 (96)	0,171
Antibiótico precoz	50/50 (100)	27/27 (100)	1.000
Infusión intensiva de sueros	49/50 (98)	27/27 (100)	0,460
Control temprano del foco infeccioso	45/50 (90)	24/27 (89)	0,879

Tabla 4 **Comparación del manejo de la sepsis en función de la afluencia a los SUH. (cont.)**

	≥ 200 visitas/día N=111 (%)	< 200 visitas/día N=136 (%)	P
Uso de biomarcadores en Urgencias	83/86 (97)	73/74 (99)	0,388
¿Existe formación en sepsis?	56/86 (65)	42/74 (57)	0,279
¿La formación es periódica?	30/56 (54)	25/42 (60)	0,557
¿Ha mejorado el manejo de la sepsis desde la implantación del CS?	82/86 (95)	72/74 (97)	0,518
¿El servicio de UCIAS forma parte del equipo/estructura del CS intrahospitalario?	61/72 (85)	33/40 (82,5)	0,759
¿Quién coordina el CS intrahospitalario?			0,010
Medicina interna	9/72 (12,5)	12/39 (31)	
Urgencias	10/72 (14)	11/39 (28)	
Medicina intensiva	36/72 (50)	13/39 (33)	
Enfermedades infecciosas	12/72 (17)	1/39 (2,56)	
Otro	5/72 (7)	2/39 (5)	

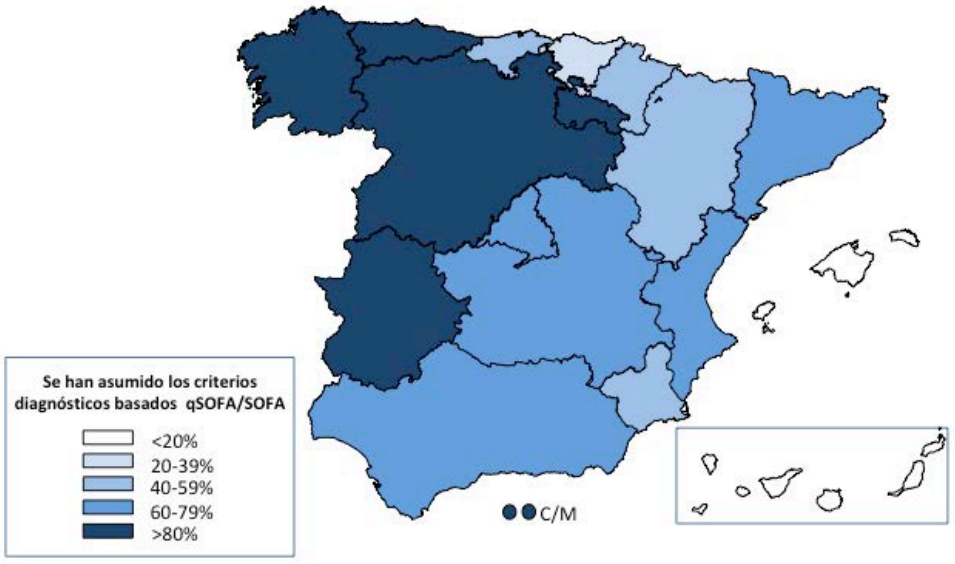


Figura 1 **Porcentaje de hospitales dentro de cada Comunidad Autónoma en la que se han asumido los criterios diagnósticos basados en el qSOFA/SOFA.**

diagnósticos imprescindibles para diagnosticar a un paciente de shock séptico [7]. Otro biomarcador de infección que en los últimos años ha tenido gran protagonismo en la valoración diagnóstica de infección bacteriana es la PCT [28]. Este biomarcador respalda el diagnóstico de sepsis [14] y tiene un mejor rendimiento que la PCR [29]. Los resultados muestran que se utiliza en menor medida al no estar disponible en uno de cada 10 hospitales, lo que entendemos que es un punto de mejora a abordar.

Otro de los aspectos analizados es la presencia de microbiólogo de guardia, lo que sólo se produce en un tercio de los hospitales. Esta falta de servicio de microbiología las 24 horas o los festivos hace que no sea posible implantar técnicas específicas de diagnóstico rápido o bien la identificación de hemocultivos

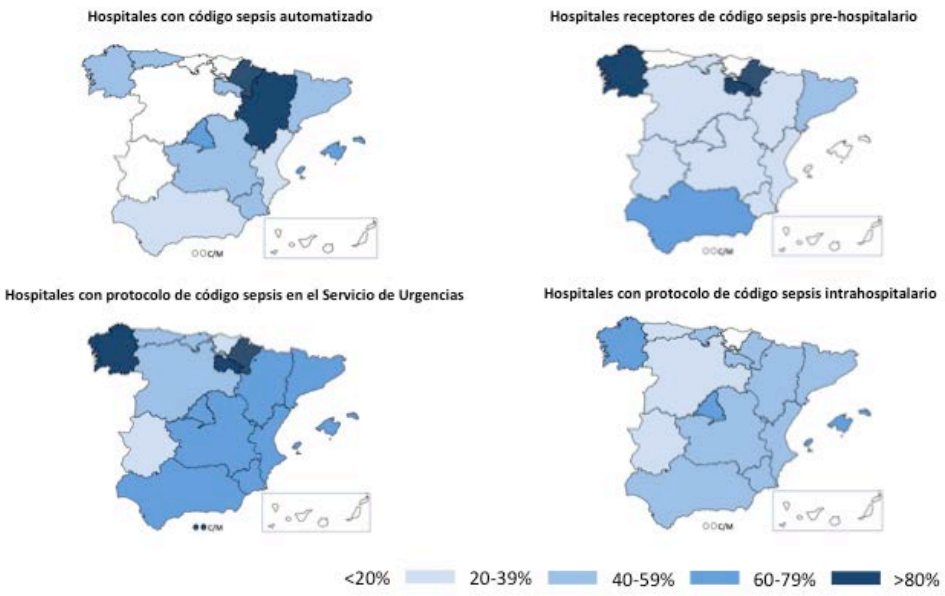


Figura 2 | **Mapa de la situación del código sepsis en función de la Comunidad Autónoma.**

positivos mediante la técnica de MALDI-TOF. Esto podría provocar que, aunque la solicitud de hemocultivos se realice de forma correcta, sólo se pueda obtener un adecuado rendimiento en horario de mañana en días laborables y no de forma continuada [4]. Esto se acentúa aún más en los hospitales pequeños.

Por último, algo que se observa en la mayoría de los hospitales es que el CS puede ser activado tanto por los profesionales de medicina como de enfermería, pero aún hay muchos hospitales en que la enfermería no puede generar esta activación. Esto posiblemente necesite ser evaluado y revisado ya que en la mayor parte de los hospitales los profesionales de enfermería son los que realizan el triaje inicial de los pacientes que acuden a Urgencias y es precisamente en esa parte de la valoración inicial del paciente cuando es fundamental el reconocimiento y activación de estos códigos de patologías tiempo-dependientes como la sepsis [30].

Nuestro estudio presenta algunas limitaciones: 1) Los resultados se basan en la opinión del responsable del SUH y no de sus profesionales, cuya opinión no siempre resulta coincidente [31]; 2) Algunos aspectos encuestados no fueron valorados de forma cuantitativa sino cualitativamente, lo que pudiera comportar que las categorías cualitativas no fuesen equidistantes; 3) El reclutamiento no fue completo, pero la participación próxima al 90% conlleva que los resultados obtenidos sean fiables y representativos de la asistencia a la sepsis en los SUH españoles. A pesar de estas limitaciones, el presente estudio ofrece una fotografía de la realidad asistencial que los SUH proporcionan a los pacientes con sospecha de sepsis y con la información obtenida detectar aquellos aspectos en los que podemos incidir para mejorar el diagnóstico y manejo precoz de la sepsis, con el consiguiente beneficio para los enfermos.

En conclusión, pensamos que aunque se está avanzando en el desarrollo de protocolos específicos para el tratamiento de la sepsis en los SUH, existe margen de mejora, sobre todo en los hospitales de menor tamaño. Creemos que la informatización y el desarrollo de alertas para el diagnóstico y tratamiento tienen aún un gran recorrido en los SUH. Aún existiendo un protocolo nacional para el desarrollo del CS [13], opinamos que cada sistema sanitario tendría que incidir en promover y crear protocolos propios basados en recomendaciones universales aplicando al mismo las peculiaridades de cada sistema.

AGRADECIMIENTOS

A Alicia Díaz, por su labor de identificación y contacto con los responsables de todos los servicios de urgencias hospitalarios españoles.

FINANCIACIÓN

Trabajo financiado por una ayuda no condicionada de Laboratorios Gilead.

BIBLIOGRAFÍA

1. Martínez Ortiz de Zárate M, González del Castillo J, Julián Jiménez A, Piñera Salmerón P, Llopis Roca F, Guardiola Tey JM, et al. ESTUDIO INFURG-SEMES: epidemiología de las infecciones atendidas

en los servicios de urgencias hospitalarios y evolución durante la última década. Emergencias 2013; 25: 368-78.

2. Bouza C, López-Cuadrado T, Saz-Parkinson Z, Amate-Blanco JM. Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011). BMC Infectious Diseases 2015; 14: 717. doi: 10.1186/s12879-014-0717-7.
3. Wang HE, Jones AR, Donnelly JP. Revised National Estimates of Emergency Department Visits for sepsis in the United States. Crit Care Med 2017; 45: 1443-9. doi: 10.1097/CCM.0000000000002538.
4. Julián-Jiménez A, Supino M, López Tapia JD, Ulloa González C, Vargas Téllez LE, González del Castillo J, et al. Puntos clave y controversias sobre la sepsis en los servicios de urgencias: propuestas de mejora para Latinoamérica. Emergencias 2019; 31: 123-35. PMID: 30963741.
5. Farreras Amez JM, Arribas Entrala B, Sarrat Torres MA, García Noain A, Caudevilla Martínez A, Colás Oros C, et al. Evaluación de los resultados antes y después de la implantación del código sepsis en Aragón. Emergencias 2017; 29: 154-60. PMID: 28825234.
6. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for sepsis and Septic Shock (sepsis-3). JAMA 2016; 315: 801-10. DOI: 10.1001/jama.2016.0287.
7. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3). JAMA 2016; 315: 762-74. doi: 10.1001/jama.2016.0288.
8. Candel FJ, Borges Sa M, Belda S, Bou G, Del Pozo JL, Estrada O, et al. Current aspects in sepsis approach. Turning things around. Rev Esp Quimioter 2018; 31: 298-315. PMID: 29938972.
9. Alquézar-Arbé A, Piñera P, Jacob J, Martín A, Jiménez S, Llorens P, et al. Impacto organizativo de la pandemia COVID-19 de 2020 en los servicios de urgencias hospitalarios españoles: resultados del estudio ENCOVUR. Emergencias 2020; 32: 320-31. PMID: 33006832.
10. González Del Castillo J, Cánora Lebrato J, Zapatero Gaviria A, Barba Martín R, Prados Roa F, Marco Martínez J. Epidemia por COVID-19 en Madrid: crónica de un reto. Emergencias 2020; 32: 191-3. PMID: 32395928.
11. Ministerio de Sanidad, Consumo y Bienestar Social. Catálogo Nacional de Hospitales 2019 (Consultado 11-6-2020). Disponible en: http://www.msssi.gob.es/ciudadanos/prestaciones/centros-ServiciosSNS/hospitales/docs/CNH2019.pdf
12. Miró O, Escalada X, Gené E, Boqué C, Jiménez Fábrega FX, Netto C, et al. Estudio SUHCAT (1): mapa físico de los servicios de urgencias hospitalarios de Cataluña. Emergencias 2014; 26: 19-34.
13. Borges Sa M, Candel González F, Ferrer Roca R, Zaragoza Crespo R. Código sepsis: documento de consenso. 2014.https://www.seguridaddelpaciente.es/en/information/publicaciones/2016/codigo-sepsis-documento-de-consenso/.
14. Palencia Herrejón E, González Del Castillo J, Ramasco Rueda F, Candel FJ, Sánchez Artola B, von Wernitz Teleki A, et al. Documento de consenso para la implantación y desarrollo del Código Sepsis en la Comunidad de Madrid. Rev Esp Quimioter 2019; 32: 400-9. PMID: 31345006.
15. Yébenes JC, Lorencio C, Esteban E, Espinosa L, Badia JM, Capdevila JA, et al. Interhospital Sepsis Code in Catalonia (Spain): Territorial model for initial care of patients with sepsis. Med Intensiva (Engl Ed). 2020; 44: 36-45. doi: 10.1016/j.medin.2019.05.008.
16. Robert Boter N, Módol Deltell JM, Casas García I, Rocamora Blanch G, Lladós Beltrán G, Carreres Molas A. La activación de un código sepsis en urgencias se asocia a una menor mortalidad. Med Clin (Barc) 2019; 152: 255-60. doi: 10.1016/j.medcli.2018.02.013.
17. García-Lopez L, Grau-Cerrato S, Frutos-Soto A, Bobillo-De Lamo F, Citores-González R, Diez-Gutiérrez F, et al. Impacto de la implantación de un código sepsis intrahospitalario en la prescripción de antibióticos y los resultados clínicos en una unidad de cuidados intensivos. Med Intensiva 2017; 41: 12-20. doi: 10.1016/j.medin.2016.08.001.
18. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, Escobar GJ. The Timing of Early Antibiotics and Hospital Mortality in sepsis. Am J Respir Crit Care Med 2017; 196: 856-63. doi: 10.1164/rccm.201609-1848OC.
19. Castro Delgado R, Arcos González P. Cardiac arrest: epidemiologic research on providing appropriate emergency management. Emergencias 2021; 33: 163-4. PMID: 33978328.
20. Castro Delgado R, Arcos González P. El análisis de la capacidad de respuesta sanitaria como elemento clave en la planificación ante emergencias epidémicas. Emergencias. 2020; 32: 157-9. PMID: 32395921.
21. Castro Delgado R, Arcos González P. Código infarto: investigación epidemiológica y en gestión para una adecuada asistencia. Emergencias 2021; 33: 163-4. PMID: 33978328.
22. Macdonald SP, Williams JM, Shetty A, Bellomo R, Finfer S, Shapiro N, Keijzers G. Review article: Sepsis in the emergency department - Part 1: Definitions and outcomes. Emerg Med Australas 2017; 29:619-25. doi: 10.1111/1742-6723.12886.
23. Ferreras JM, Judez D, Tirado G, Aspiroz C, Martínez-Álvarez R, Dorado P, et al. Implementación de un sistema de alarmas automático para la detección precoz de los pacientes con sepsis grave. Enferm Infecc Microbiol Clin 2015; 33: 508-15. doi: 10.1016/j.eimc.2015.01.002.
24. Serafim R, Gomes JA, Salluh J, Povoa P. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of sepsis and Prediction of Mortality: A Systematic Review and Meta-Analysis. Chest 2018; 153: 646-55. doi: 10.1016/j.chest.2017.12.015
25. Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE, et al. Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection: A Systematic Review and Meta-analysis. Ann Intern Med 2018; 168: 266-75. doi: 10.7326/M17-2820.
26. Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in pacients admitted acutely to hospital: a systematic review. Scand J Trauma Resus Emerg Med 2011; 19: 74. doi: 10.1186/1757-7241-19-74.
27. Julián-Jiménez A, Candel-González FJ, González del Castillo J. Utilidad de los biomarcadores de inflamación e infección en los servi-

cios de urgencias. Enferm Infecc Microbiol Clin 2014; 32: 177-90. DOI: 10.1016/j.eimc.2013.01.005.

28. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med 2019; 57:1308-18. doi: 10.1515/cclm-2018-1181.
29. Saeed K, González Del Castillo J, Backous C, Drevet S, Ferrer R, Gavazzi G, et al Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship? Int J Antimicrob Agents 2019; 54: 686-96. doi: 10.1016/j.ijantimicag.2019.07.016.
30. Sáchez Bermejo R, Cortés Fadrique C, Rincón Fraile B, Fernández Centeno E, Peña Cueva S, De las Heras Castro EM. El triaje en urgencias en los hospitales españoles. Emergencias 2013; 25: 66-70. doi: 10.1016/j.diagmicrobio.2014.09.028.
31. Jacob J, Gené E, Alonso G, Rimbau P, Zorrilla J, Casarramona F, et al. Estudio SUHCAT-5: comparación de la percepción de la calidad de los servicios de urgencias de Cataluña entre los profesionales sanitarios y sus responsables. Emergencias 2018; 30: 45-9. PMID: 29437310.

Official journal
of the Spanish Society
of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/153.2021

Emilio Garcia-Moran[1]
Marta Hernández[2]
David Abad[2]
José M. Eiros[1]

Putative Secondary Structure at 5'UTR as a Potential Antiviral Target against SARS-CoV-2

[1]Centro Nacional de la Gripe. Microbiology Department, Faculty of Medicine, Valladolid, Spain
[2]Laboratory of Microbiology and Molecular Biology, Instituto Tecnologico Agrario de Castilla y Leon, Valladolid, Spain

Article history
Received:26 October 2021; Accepted: 20 November 2021; Published: 15 December 2021

ABSTRACT

SARS-CoV-2 is an enveloped positive-sense single-stranded RNA coronavirus that causes COVID-19, of which the current outbreak has resulted in a high number of cases and fatalities throughout the world, even vaccine doses are being administered. The aim of this work was to scan the SARS-CoV-2 genome in search for therapeutic targets. We found a sequence in the 5'UTR (NC_045512:74-130), consisting of a typical heptamer next to a structured region that may cause ribosomal frameshifting. The potential biological value of this region is relevant through its low similarity with other viruses, including coronaviruses related to SARS-CoV, and its high sequence conservation within multiple SARS-CoV-2 isolates. We have predicted the secondary structure of the region by means of different bioinformatic tools. We have suggested a most probable secondary structure to proceed with a 3D reconstruction of the structured segment. Finally, we carried out virtual docking on the 3D structure to look for a binding site and then for drug ligands from a database of lead compounds. Several molecules that could be probably administered as oral drugs show promising binding affinity within the structured region, and so it could be possible interfere its potential regulatory role.

Keywords: SARS-CoV-2; frameshifting; 5'UTR; pseudoknot; molecular docking.

Estructura secundaria en 5'UTR como diana antiviral contra el SARS-CoV-2

RESUMEN

El SARS-CoV-2 es un coronavirus de ARN monocatenario de sentido positivo envuelto que causa COVID-19, del cual el brote actual ha provocado una gran cantidad de casos y muertes en todo el mundo, incluso cuando se están administrando dosis de vacunas. En este trabajo hemos escaneado el genoma del SARS-CoV-2 en busca de dianas terapéuticas. Encontramos una secuencia en el 5'UTR (NC \ _045512: 74-130), que consiste en un heptámero típico junto a una región estructurada que puede causar cambios en la pauta de lectura. El valor biológico potencial de esta región es relevante debido a su baja similitud con otros virus, incluidos los coronavirus relacionados con el SARS-CoV, y su alta conservación de secuencia dentro de múltiples aislados de SARS-CoV-2. Hemos predicho la estructura secundaria de la región mediante diferentes herramientas bioinformáticas. Hemos sugerido una estructura secundaria más probable para así proceder al acoplamiento virtual en la estructura 3D para buscar un sitio de unión y luego ligandos de fármacos. Hemos encontrado varias moléculas que probablemente podrían administrarse como fármacos orales muestran una afinidad de unión prometedora dentro de la región estructurada, por lo que es posible que interfieran en su posible función reguladora de la replicación viral.

Palabras clave: SARS-CoV-2, cambios en la pauta de lectura, 5'UTR, pseudonudo, acoplamiento virtual

INTRODUCTION

On March 11th, the World Health Organization (WHO) declared COVID-19 a clinical pandemic (primarily pneumonia and gastroenteritis) caused by the SARS-CoV-2 virus. As of end October 2021 the pandemic outbreak has caused almost five million deaths worldwide, although almost 7 million peo-

Correspondence:
Emilio Garcia-Moran
Centro Nacional de la Gripe. Microbiology Department, Faculty of Medicine, 47005 Valladolid, Spain
E-mail: egarmo@egarmo.com

ple are vaccinated. SARS-CoV-2 belongs to the *Coronaviridae* family and is related to SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV (79% and 50% genomic similarity, respectively). SARS-CoV caused an epidemic outbreak in 2003 and MERS caused an outbreak in 2012 [1]. Those three viruses belong to the *Betacoronavirus* genus. Coronaviruses cause zoonotic infections, so they may spill over from a host species to a different one through small changes in their genome. SARS-CoV-2 demonstrated a high genetic similarity (more than 85%) to a virus group known as SARS related coronavirus (SARSr-CoV), which are isolated from animal hosts, including *Hipposideros* bats and pangolins (*Manis javanica*). These species seem to be candidates as intermediate hosts for SARS-CoV-2 [2,3].

These viruses have a positively translated single strand RNA genome and they use programmed –1 ribosomal frameshifting (–1 PRF) to direct the synthesis of immediate early proteins that prepare the infected cell for takeover by the virus. Frameshifting is a smart mechanism for the translation of a genomic sequence into two different proteins by moving the translation frame one position in the union between RNA and the ribosome [4]. A typical frameshifting signal has two essential elements: a characteristic heptanucleotide called the 'slippery' sequence, at which the ribosome-bound tRNAs slip into the -1 frame, and an adjacent mRNA secondary structure that stimulates this slippage process. The intermediate sequence between these two elements also has a typical size of less than twelve nucleotides. Often the secondary structure is more complex than a simple stem-loop between palindromic sequences, expanding into pseudoknots [5]. In terms of structure, a pseudoknot forms upon the base-pairing of a single-stranded region of RNA in the loop of a hairpin to a stretch of complementary nucleotides elsewhere in the RNA chain.

A set of bioinformatic tools has already been developed to predict these structures [6]. The mechanism of action of pseudoknots is not completely understood; some authors suggest that it appears to be linked to the helicase activity of the ribosome. When pseudoknots are located in coding regions, they modulate the elongation and termination steps of translation: the ribosome is able to switch from the zero reading frame to the –1 frame and translation continues in the new frame. When pseudoknots are in non-coding regions, they act on the regulation of the initiation of protein synthesis and on template recognition by the viral replicase guiding viral replication and packaging [7].

All coronaviruses have been reported to utilize programmed –1 ribosomal frameshifting to control the expression of their proteins. In 2005, Plant et al. [8] identified a three-stemmed mRNA pseudoknot inducing an efficient -1 ribosomal frameshift in the SARS-CoV genome. By this mechanism, the virus may produce a fusion protein that overlaps the regions ORF1a and ORF1b. This element encodes an ORF1ab polyprotein involved in ablating the host cellular innate immune response. Mutations affecting this structure decreased the rates of -1 PRF and had deleterious effects on the virus propagation. Recently, Kelly et al. [9] described the same pseudoknot in SARS-CoV-2, and they demonstrated frameshifting. This area is highly conserved between SARS-CoV and SARS-CoV-2, as there is only one single nucleotide difference, a C to A substitution at position 13,533 bp.

The frameshifting regions could be used as a target to fight viral infection [9]. Starting with early studies, point mutations at the slippery sequence have proved to have an important effect on viral replication [8]; thus, they can be also interesting points in the engineering of an attenuated virus for vaccine development. The inhibition of these regions by peptide antisense oligomers was studied by Neuman et al. [10]. After several passages in cell culture, virions escape the inhibition of replication but show attenuated forms. Rangan et al. [11], described highly structured areas of RNA that might be less accessible to complementary oligomers, but these convoluted areas would provide small binding sites for conventional drug molecules; therefore, a combination of scanning for structure and sequence conservation may be appropriate to find therapeutic targets. Previous studies using *in silico* methods found drug-like molecules that would inhibit SARS-CoV replication by action on the frameshifting region at the overlap between ORF1a and ORF1b [12]. The same molecule has been shown to affect replication in SARS-CoV-2 [9].

In this work, we scanned the SARS-CoV-2 genome to seek for novel likely critical areas for virus replication focusing on frameshifting predictors. We explored the likely biological relevance of this feature through the study of sequence conservation and its suitability as a potential drug target by the analysis of the structural properties and the drug docking prediction.

MATERIAL AND METHODS

Genomewide frameshifting signal search. A prediction of the relevant sequence and structures in the viral reference genome for SARS-CoV-2 (NC 045512) [13] was performed using the KnotInFrame tool [14]. The output determined the sequence and position of slippery sequences and nearby pseudoknots, since both criteria are needed to predict frameshifting. Our focus on a particular region was established by combining KnotInFrame output with biological knowledge. We focused on previously undescribed frameshifting regions and the likely regulatory roles of UTR regions. Once a sequence of interest met these criteria, an inspection of the predicted secondary structure was achieved with additional tools ipknot [15] and RNAfold from Vienna Suite [16]. The secondary structure for the segment of interest in dot bracket notation was chosen from the inspection of the overall conformation of the 5'UTR and assuring to include the slippery region. The likelihood of the secondary structure was assessed by computing the minimum free energy (MFE) of a large number of random sequences of SARS-CoV-2 of the same length as the sequence of interest into mFold, in order to obtain an empirical distribution of MFE and so assess how dominant the proposed structure would be [17].

Conservation of the sequence of interest. Sequence conservation was assessed for the sequence of interest deter-

mined in the previous step as a reliable trait of biological relevance. The conservation of the sequence of interest was evaluated in two steps. First, the conservation between SARS-CoV-2 and other human and animal hosted coronavirus genomes was studied by the computation of a cladogram and by the search for the alignment of the sequence of interest against a comprehensive viral database. A total of 21 high quality genomes from coronavirus hosted in humans and other species were selected based on subjective criteria regarding variability and relevant facts to build a cladogram. The genomes were downloaded from GenBank and aligned with Clustal Omega [18] using the default parameters. The cladogram was constructed using a maximum likelihood estimate with FastTree [19], under a GTT model of nucleotide evolution. The package ggtree [20] was used in R [21] to generate the graphic of the cladogram and the multiple sequence alignment (MSA). In addition to this alignment of the SARS-CoV-2 and another 20 coronavirus genomes, the sequence of interest was examined by ViroBLAST [22]. This tool provides a blastn [23] alignment with a comprehensive database of all types of virus, so that we would assess any casual homology with any other virus. Secondly, we evaluated the conservation of the sequence of interest within SARS-CoV-2 isolates from different geographic locations since the onset of the pandemic. We took advantage of the fast contribution of genomes into the GISAID database. We filtered the genomes in the database in order to retain only high quality records (length greater than 29,000 nt and with a low number of undetermined positions). The number of variant site strains was assessed by blastn [23], making the distinction of variants at the whole 5'UTR region (1-265 nucleotide positions); and the number of variants at the position of the sequence of interest. Further individual inspections of mismatched genomes were conducted to ensure whether the variation was not due to technical sequencing reasons.

Prediction of 3D structure and molecular docking. Upon consideration of different alternatives, the structure of the sequence of interest in dot-bracket notation and the underlying nucleotide sequence were imported into Rnacomposer [24] to obtain a 3D structure prediction in .pdb format. The file in .pdb format was used as input for the virtual scan for active sites. This task was carried out using Autodock tools suite [25]. This suite comprises the AutoGrid and Autoligand tools for the search of active sites in a molecular 3D structure. A combination of manual selection of the region of interest and automatic search space by the tools was used to obtain the coordinates and dimensions of a putative active site. These data were used as inputs for the molecular docking by the Autodock Vina tool. The virtual docking tested the binding of a set of molecules specially selected for drug screening: the NCBI maximum diversity set II. The affinity of molecules to bind the active site was assessed by the minimum free energy in Kcal/mol.

RESULTS

Frameshifting prediction. We used Knotinframe program [14] to detect cis-acting signals, the nucleotide sequence and the position of the heptameric slippery sites and near pseudoknots as prediction for –1 PRF. A list of genomic regions of SARS-CoV-2 (NC 045512.2) where a frameshifting signal was predicted by the KnotInFrame program is shown in Table 1. The stability of every predicted structure is also indicated by the MFE value, on the rightmost column. A more negative value of MFE represents a more stable and likely to be a functional structure. This value is mainly dependent on the length of the sequence. The pseudoknot we propose associated with the pattern sequence at position 76 (UUUAAAA) that was identified as –1 PRF, is ranked fourth and exhibit the lowest MFE

Table 1 **Summary of the output of KnotInFrame tool on NC_ 045512.2 genome.**

Slippery sequence	Slippery pos.	Pseudoknot start	Pseudoknot end	Length	Deltarel	MFE
TTTAAAC	13462	13469	13549	80	0.126	-34.80
GGGTTTA	4261	4268	4328	60	0.092	-15.60
AAATTTG	6071	6078	6158	80	0.076	-16.10
TTTAAAA[a]	76	83	123	40	0.070	-14.00
GGGTTTT	13348	13355	13475	120	0.051	-34.90
GGGTTTG	8183	8190	8270	80	0.049	-15.10
TTTAAAT	4264	4271	4331	60	0.047	-15.60
CCCAAAA	20646	20655	20773	120	0.046	-29.00
TTTAAAA	6514	6521	6621	100	0.038	-19.40
TTTAAAC	20817	20824	20924	100	0.035	-30.20
TTTTTTT	11076	11085	11183	100	0.035	-19.60

[a]The line in bold face was chosen as the sequence of interest. MFE: minimum free energy

```
70--------80--------90--------100-------110-------120-------130 bp position
CGAACUUUAAAAUCUGUGUGGCUGUCACUCGGCUGCAUGCUUAGUGCACUCAC
.........(((((((..((.((((.(((.....))).))))))..))))))        Rangan
.............(((((((((.....)))))))))((...[[)).... ]]        IPknot
...........(((((((((((...[[))))))(((.....]]))).....)))))).... IPknot-cutoff
.............(((((((((.....)))))))))((.....)).....          RnaFold
xxxxxxxxxxxx....[[[[[[[[.{{{{]]]]]]]].....}}}}.....x         KnotInFrame
```

Figure 1 | **Segment of 5'UTR NC 045512 sequence and different predicted secondary structures. The slippery heptamer is highlighted in yellow.**

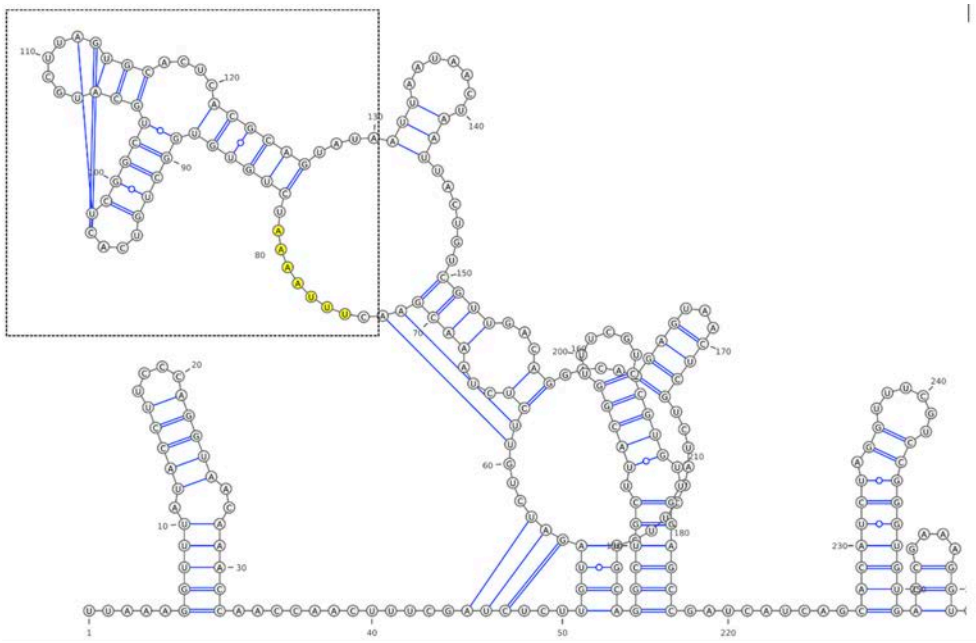


Figure 2 | **Secondary structure of 5'UTR region of NC 045512 as predicted by IPKnot. Region of interest framed on the top left. Slippery sequence in yellow.**

value among the predictions on the whole genome. However, all the other structured sequences are longer and this causes their stability not to be so much significantly higher than the region we propose associated with the slippery sequence located at position 76.

RNA 2D structure. The selected predicted frameshifting region clearly falls into the 5'UTR of NC_045512.2 reference genome [14], which spans from 1 to 265 nt as the first start codon for the coding sequence is at 266 position in SARS-CoV-2. However, if –1 PRF occurs within the 5'UTR region, probably at the U nucleotide at position 95 nt, then there is an upstream AUG codon at position 107 that can act as start codon and viral translation might be altered. The sequence of interest spanning from position 74:130 was selected and it is shown in Figure 1 along with the secondary structure as predicted by different programs in dot bracket notation. The IPknot tool [15] has been used in two fashions, firstly by the only input of the sequence of interest and secondly, by the input of the whole 5'UTR region, and then cutting out the prediction for positions 7:130. In both cases, IPknot predicts a knotted structure just downstream of the slippery region (the pattern of opening and closing brackets do not match, meaning that stem-loops bind to outer regions). Interestingly, the prediction we obtained using IPknot fully agrees with the prediction obtained recently in that genomic area using the Rosetta tool [11].

Similarly, the secondary structure of the whole 5'UTR regions was also obtained by IPknot tool and the graphical representation of that secondary structure using the VARNA software [26] is shown in Figure 2. Upon the inspection of the secondary structure, a sequence of interest spanning from position 74:130 was selected (left top corner) to include the

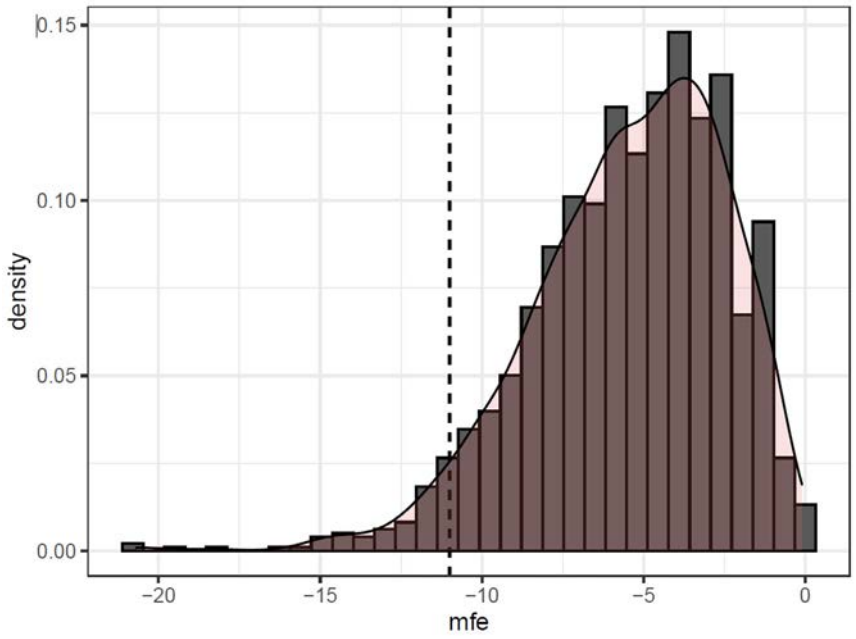


Figure 3 The histogram and density curve of the minimum free energy values of random sequences from NC 45512.2 of the same length as the sequence of interest. The vertical line at -11 Kcal/mol shows the computed MFE for the sequence of interest.

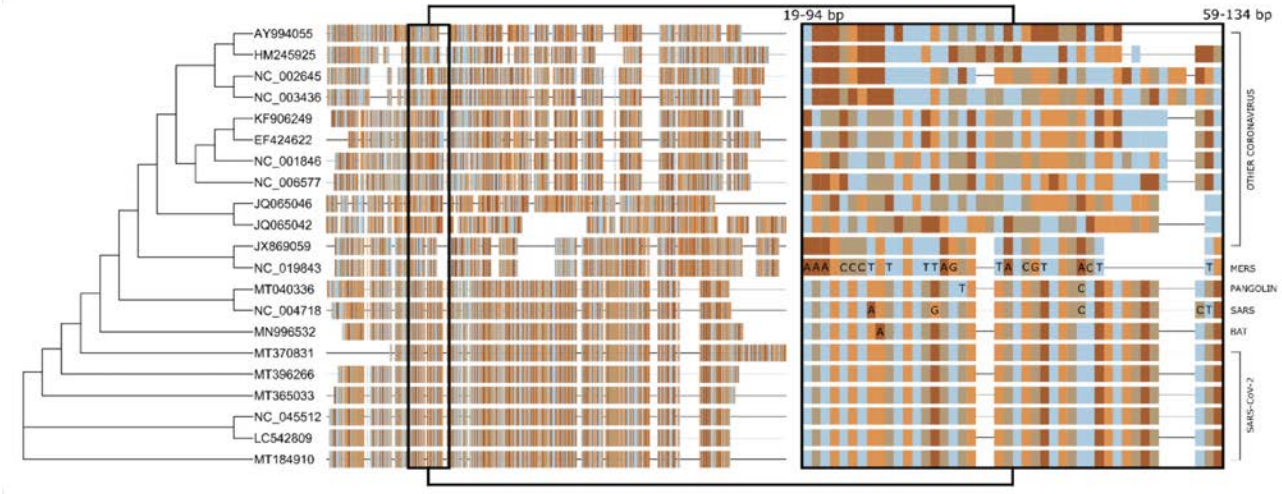
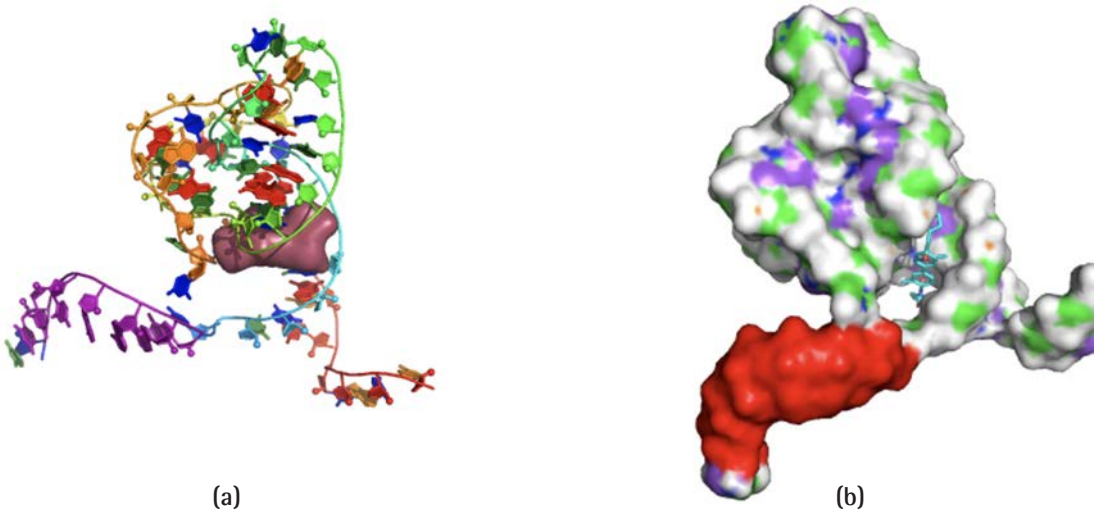


Figure 4 A cladogram and multiple sequence alignment. The middle part shows the alignment of the region in 21 coronaviruses. On the left, are shown the groups of sequences in terms of similarity. A zoomed in view on the region of the sequence of interest is shown on the right.

slippery sequence and neighbouring structured segment. The sequence (positions 74—130) was also used to proceed with the analysis so that it includes the slippery region and the structure of the stem and loop and the pseudoknot.

In order to test the probability of the predicted secondary structure as indicated by its computed MFE, we analyzed 1,509 random sequences from NC_45512.2 of the same length as the sequence of interest. Their MFE values were computed by mFold [17] to obtain an empirical distribution. The predicted value for the sequence of interest (-11 Kcal/mol) was ranked



(a) (b)

Figure 5 (a) Graphical representation of the nucleotide backbone of the sequence of interest. The sequence of interest is shown from the 5' end (left) to the 3' end (right). The rounded purple volume in the middle shows the active site as predicted by the AutoDock suite tools. The slippery sequence is on the left bottom, in purple colour, the rest of nucleotide pieces are coded according to chemical composition. (b) Side view of the sequence of interest in a surface representation. The red area on the left shows the slippery sequence. The active ligand site holds one of the best matches: NSC308835/pubChem328761 (see Table 3) in its docked position.

Table 2 List of similar hits to NC 045512:74-130 in Viroblast database.

Host	GenBank accession no.	Date (year)	Score	Identities (Query length)	Percentage	Expect
Rhinolophus pusillus	JX993987.1	2011	86.0	52/55 (57)	95	1e-15
Rhinolophus sinicus	KJ473814.1	2013	86.0	53/57 (57)	93	1e-15
Rhinolophus sinicus	MG772933.1	2017	86.0	53/57 (57)	93	1e-15
Rhinolophus sinicus	MG772934.1	2017	86.0	53/57 (57)	93	1e-15
Mus musculus	HQ890526.1	2008	80.6	52/57 (57)	91	5e-14
Mus musculus	HQ890527.1	2008	80.6	52/57 (57)	91	5e-14
Mus musculus	HQ890528.1	2008	80.6	52/57 (57)	91	5e-14
Mus musculus	HQ890529.1	2008	80.6	52/57 (57)	91	5e-14
Mus musculus	HQ890530.1	2008	80.6	52/57 (57)	91	5e-14
Mus musculus	HQ890531.1	2008	80.6	52/57 (57)	91	5e-14

within empirical distribution of the MFE values. The histogram and frequency curve of this distribution is shown in Figure 3. The vertical line is set at -11 Kcal/mol. Clearly, few random sequences show this value. This value was at the top 5% of the negative endo of the distribution. This reveals that the predicted structure is fairly stable in relation to other segments of NC_45512, and supports that this sequence may occur in the predicted form of a stem-loop with outer bindings to form a pseudoknot and thus, along with the immediate slippery sequence form a frameshifting signal.

Genomic similarity. The conservation of the 74--130 region among *Coronaviridae* family is shown in Figure 4. Interestingly, while this region was identical in all the isolates from SARS-CoV-2 including isolates from human patients from distant geographical localizations (MT370831, New York; and

Table 3 Results of docking of lead compounds from NCI diversity set II against the predicted active site in the sequence of interest.

NSC id	pubChem id	MFE[a]	Molecular formula	H bond donors	H bond acceptors	Active torsions	Mol weight
293778	325266	-12.2	C40H26N4S	0	5	2	594.7
308835	328761	-11.1	C30H32N2O4	0	4	0	484.6
61610	247228	-11.1	C34H24N6O2	4	4	4	548.6
37641	235856	-11	C29H33FO6	2	7	4	496.6
319990	330740	-10.7	C23H18N6O2S2	4	6	4	474.6
93354	261360	-10.6	C28H33NO2S	1	4	1	447.6
122819	452548	-10.5	C32H32O23S	3	14	7	656.7
37553	235811	-10.5	C30H28N4O2	2	2	2	476.6
37641	235856	-10.5	C29H36FO6	2	7	4	496.6

[a]Values of predicted MFE in Kcal/mol. MFE: minimum free energy

LC542809, Japan) and from animals suspected to be infected from humans (MT396266, farm mink; and MT365033, zoo tiger), increasing differences were observed in other *Coronaviridae*. A minor difference in one nucleotide was found in a bat sequence (MT996532), while the differences increased in the pangolin hosted virus, and SARS-CoV-1 (NC_004718, Tor2 strain). Subsequently, we also tested the sequence of interest for similarity to other viruses on the Viroblast database [22]. The search parameters were kept at nominal values except for the word length, which was changed from ten to seven to increase the likelihood of matching slippery sequences. Viroblast search yielded 10 hits derived from two sources (Table 2): the top four hits were coronaviruses isolated in China from different species of bat *Rhinolophus pusillus/sinicus* between 2011 and 2017 and the latest hits a mouse-adapted laboratory model derived from SARS-CoV (consecutive GenBank accession numbers from HQ890526 to HQ890531.1; although these isolates were sampled from the Urbani strain GenBank AY278741 rather than Tor2). Finally, we evaluated the conservation of the sequence of interest among clinical SARS-CoV-2 isolates. The 5'UTR (1-265 nucleotide positions) of NC_045512.2 was searched using BLASTN [23] analysis against 54,466 high quality filtered genomes (out of 84,140) retrieved from GISAID on the 21st of August, 2020. While, only a 19,8% of the genomes (10,789 out of 54,466) had a 100\% identity in the complete 5'UTR, the 74—130 region was highly conserved, as it was 100\% identical in 99.3 % of SARS-CoV-2 genomes tested (53,077 out of 53,456).

RNA 3D structure. In order to carry out molecular docking on potential active sites of the sequence of interest was continued the nucleotide sequence in the Figure 1 and the selected region of the secondary structure in Figure 2 as inputs into RNAcomposer [24] to obtain a .pdb file of the nucleotide sequence. The results of the predicted 3D structure and the possible location of a drug binding site are shown in Figure 5. The volume of the binding site is the result of the exploration with Autodock tools. The coordinates of the binding site were obtained in .pdb format and they were passed into Autodock Vina (the exhaustiveness search parameter at a default value of eight; and the random seed sequence was fixed) [25]. The results of the docking by Autodock Vina against the lead compounds from the NCBI Maximum Diversity set II are shown in Table 3. The Autodock Vina predicted the affinity of the lead compounds by the computation of the MFE. As more negative values of MFE mean higher binding affinities, so the lead compounds were ranked by this value. The number of hydrogen bond donors and acceptors and the molecular weight in g/mol are annotation data from PubChem. These data show how likely a compound is to be used as an oral drug [27].

DISCUSSION

This study has revealed a previously unnoticed feature in the SARS-CoV-2 genome, which is likely to play a biological role on account of the remarkable conservation of its sequence and stability of the structure. The close occurrence of the slippery sequence and a likely stable pseudoknot suggests that this may be an area of frameshifting, in addition to the previously described overlapping region of ORF1a and ORF1b, where frameshifting has been proven for SARS-CoV [8] and also present in SARS-CoV-2 [9]. We focused on a different region, previously unnoticed in the 5'UTR. The fact that no protein may be linked with the sequence may argue against frameshifting, as may that of the overlap between ORF1a and ORF1b. Supporting the role of 5'UTR, Zhu et al. [28] demonstrated that different natural deletions in the 5'UTR of FMDV (foot-and-mouth disease virus) markedly affected the pathogenicity and species tropism of the virus. Frameshifting linked with 5'UTR has been described in HIV-1 [29], and in this case the structure next to the slippery sequence is a stem and loop, without additional pseudoknotting.

Another important endeavour of this work is to consider this RNA structured area as a useful target for feasible drug

intervention. Puzzlingly, the description of a possible drug against the pseudoknot involved in frameshifting between ORF1a and ORF1b in SARS-CoV did not progress to an actual drug for use in health care [12,30], probably due to the lag in time of this discovery after the 2003 SARS-CoV outbreak. The same molecule that was found to inhibit viral replication of SARS-CoV appears to be effective against SARS-CoV-2 [9].

Rangan et al. [11] performed a wide analysis on the SARS-CoV-2 and SARSr-CoV genomes, and they classified multiple regions in terms of the conservation and RNA structure. In agreement with our approach, they consider that structured regions would be ideal targets for small drug molecules. In Table 2 (eighth row) of their article, they describe, among others, sequence 40:157 of NC_045512-2 as highly conserved and structured. We reproduce in Figure 1 their proposal of structure for our region of interest. The result of the alignment of our sequence of interest against the Viroblast database showed that the sequence may have been close to SARS-CoV as described in 2003 [31]. We found two pathways of highly similar sequences; coronaviruses isolated from bats in the following years and from laboratory-derived strains developed to create a mouse-adapted model from the Urbani strain of SARS-CoV-2. Although outside of this work, these findings support the role of bats as intermediate hosts between SARS-CoV and SARS-CoV-2, and the possibility that some unrecognized variation in strains of SARS-CoV would manifest relevant features as with the sequence which we describe.

A limitation of our work is that it was restricted to computational analysis. This shortcoming is likely more relevant when it comes to the determination of the tridimensional structure of RNA and its subsequent docking. The determination of the crystal structure 3D prediction and drug docking has been developed for proteins rather than RNA. One of the features of RNA that makes docking difficult is its flexibility. However, successful discovery of ligands against SARS-Cov-2 pseudoknot by a computed 3D structure has been described before [12,30]. Clinical evidence of pharmacological actions against RNA viral genomes was achieved by drugs such as sofosbuvir (tradename Sovaldi) against Hepatitis C Virus (HCV). These drugs are described as nucleotide analogues. They bind to the target region as a complementary sequence would do but they differ from short chains of nucleotides so that they may resist lytic enzymes.

Our screening for drug ligands was an exploratory analysis, as it was limited to 1,507 compounds from NCBI maximum diversity set II. In Table 3 several compounds have a MFE lower than -10 Kcal/mol. This suggests that a search against a larger catalog would yield multiple candidates. Several compounds on the Table 3 can meet the criteria to be orally useful drugs according to Lipinski's rule of five [29]. We point out that the compound ranked second in terms of MFE affinity: NSC 308835 as it meets every Lipinski's criterion. The next best compound did not meet that molecular weight, which should be less than 500 g/mol, though by a small margin. This fact does not preclude oral activity. NSC61610 was given orally, once a day to mice in an experimental model of H1N1 influenza infection [32]. The mice had less mortality and the response was better than with tamiflu after the sixth day of infection. However, that mechanism of action is unrelated to interactions with viral RNA, as NSC61610 acts as a modulator of the immune response.

In conclusion, we have identified a relevant sequence in the 5'UTR region of SARS-CoV-2. It displays traits which have a high potential for playing an important role, either through frameshifting or other mechanism. A remarkable conservation within SARS-CoV-2 isolates strongly supports a biological role for this sequence. Our analysis of the drug susceptibility of this sequence is hindered by the inconsistent predictions of bioinformatic tools. It is however very likely that a strong structure of this area will allow effective action of relatively simple drug molecules.

ACKNOWLEDGMENTS

We kindly acknowledge Dr. Nigel Cook for English revision.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Coleman CM, Frieman MB. Emergence of the Middle East Respiratory Syndrome coronavirus. PLoS pathogens. 2013;9:e1003595. doi: 10.1371/journal.ppat.1003595.
2. Wang H, Li X, Li T, Zhang S, Wang L, Wu X, Liu J. The genetic sequence, origin, and diagnosis of SARS-CoV-2. Eur. J. Clin. Microbiol. Infect. Dis. 2020; 39(9):1629-35. doi: 10.1007/s10096-020-03899-4.
3. Han GZ. Pangolins Harbor SARS-CoV-2-Related Coronaviruses. Trends Microbiol., 2020,28(7):515-17. doi: 10.1016/j.tim.2020.04.001.
4. Jacks T, Madhani HD, Masiarz FR, Varmus HE. Signals for ribosomal frameshifting in the Rous sarcoma virus gag-pol region. Cell. 1988;55(3):447-58. doi: 10.1016/0092-8674(88)90031-1.
5. Brierley I, Pennell S, Gilbert RJC. Viral RNA pseudoknots, versatile motifs in gene expression and replication. Nat Rev Microbiol. 2007;5(8):598-610. doi: 10.1038/nrmicro1704.
6. Lim CS, Brown CM. Know your enemy, Successful bioinformatics approaches to predict functional RNA structures in viral RNAs. Front Microbiol. 2018;4;8:2582. doi: 10.3389/fmicb.2017.02582.
7. Fehr AR, Perlman S. Coronaviruses, an overview of their replication and pathogenesis. Methods in molecular biology (Clifton, N.J.). 2015;1282:1-23. doi: 10.1007/978-1-4939-2438-7_1.
8. Plant EP, Perez-Alvarado GC, Jacobs JL, Mukhopadhyay B, Hennig

M, Dinman JD. A three-stemmed mRNA pseudoknot in the SARS coronavirus frameshift signal. PLOS Biology. 2005;3(6):e172. doi: 10.1371/journal.pbio.0030172.

9. Kelly JA, Olson AN, Neupane K, Munshi S, San Emeterio J, Pollack L, Woodside MT, Dinman JD. Structural and functional conservation of the programmed -1 ribosomal frameshift signal of SARS coronavirus 2 (SARS-CoV-2). J. Biol. Chem. 2020;31;295(31):10741-48. doi: 10.1074/jbc.AC120.013449.
10. Neuman BW, Stein DA, Kroeker AD, Churchill MJ, Kim AM, Kuhn P, Dawson P, Moulton HM, Bestwick RK, Iversen PL, Buchmeier MJ. Inhibition, escape, and attenuated growth of severe acute respiratory syndrome coronavirus treated with antisense morpholino oligomers. J. Virol. 2005;79(15):9665-76. doi: 10.1128/JVI.79.15.9665-9676.2005.
11. Rangan R, Zheludev IN, Das R. RNA genome conservation and secondary structure in SARS-CoV-2 and SARS-related viruses, a first look. RNA. 2020;26(8):937-59. doi: 10.1261/rna.076141.120.
12. Park H-J, Park S-J. Virtual Screening for RNA-Interacting Small Molecules. In: Dinman J. (eds) Biophysical approaches to translational control of gene expression. Biophysics for the Life Sciences, vol 1. Springer, New York, NY. 2012;1:235-52. doi:10.1007/978-1-4614-3991-2_12.
13. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, Hu Y, Tao Z-W, Tian J-H, Pei Y-Y, Yuan M-L, Zhang Y-L, Dai F-H, Liu Y, Wang Q-M, Zheng J-J, Xu L, Holmes EC, Zhang Y-Z. A new coronavirus associated with human respiratory disease in china. Nature. 2020;579(7798):265-69. doi: 10.1038/s41586-020-2008-3.
14. Theis C, Reeder J, Giegerich R. Knotinframe, prediction of -1 ribosomal frameshift events. Nucleic Acids Res. 2008;36(18):6013-20. doi: 10.1093/nar/gkn578.
15. Sato K, Kato Y, Hamada M, Akutsu T, Asai K. IPknot, fast and accurate prediction of RNA secondary structures with pseudoknots using integer programming. Bioinformatics. 2011;27(13):i85-93. doi: 10.1093/bioinformatics/btr215.
16. Lorenz R, Bernhart SH, zu Siederdissen HC, Tafer H, Flamm C, Stadler PF, Hofacker IL. ViennaRNA package 2.0. Algorithms for molecular biology. 2011; 6:26 doi: 10.1186/1748-7188-6-26.
17. Gruber AR, Lorenz R, Bernhart SH, Neubouck R, Hofacker IL. The Vienna RNA websuite. Nucleic Acids Res. 2008; 36(Web Server issue):W70-74. doi: 10.1093/nar/gkn188.
18. Sievers F, Wilm A, Dineen D, Gibson TJ, Karplus K, Li W, Lopez R, McWilliam H, Remmert M, Soding J, Thompson JD, Higgins DG. Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega. Mol Syst Biol. 2011;7:539. doi: 10.1038/msb.2011.75.
19. Price MN, Dehal, PS, Arkin AP. FastTree, computing large minimum evolution trees with profiles instead of a distance matrix. Mol Biol Evol. 2009;26(7):1641-50. doi: 10.1093/molbev/msp077.
20. Yu G. Using ggtree to visualize data on tree-like structures. Curr Protoc Bioinformatics. 2020;69(1):e96. doi: 10.1002/cpbi.96.
21. R Core Team. R, A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2017.
22. Deng W, Nickle DC, Learn GH, Maust B, Mullins JI. Viroblast, a standalone blast web server for flexible queries of multiple databases and user's datasets. Bioinformatics. 2007;23(17):2334-6. doi: 10.1093/bioinformatics/btm331.
23. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool. J Mol Biol. 1990;215(3):403-10. doi: 10.1016/S0022-2836(05)80360-2.
24. Popenda M, Szachniuk M, Antczak M, Purzycka KJ, Lukasiak P, Bartol N, Blazewicz J, Adamiak RW. Automated 3D structure composition for large RNAs. Nucleic Acids Res. 2012;40(14),e112. doi: 10.1093/nar/gks339.
25. Trott O, Olson AJ. AutoDock Vina, improving the speed and accuracy of docking with a new scoring func tion, efficient optimization, and multithreading. J Comput Chem. 2010;31(2),455-61. doi: 10.1002/jcc.21334.
26. Darty K, Denise A, Ponty Y. VARNA, Interactive drawing and editing of the RNA secondary structure. Bioinformatics. 2009;25(15),1974-75. doi: 10.1093/bioinformatics/btp250.
27. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26. doi: 10.1016/s0169-409x(00)00129-0.
28. Zhu Z, Yang F, Cao W, Liu H, Zhang K, Tian H, Dang W, He J, Guo J, Liu X, Zheng H. The pseudoknot region of the 5' untranslated region is a determinant of viral tropism and virulence of foot-and-mouth disease virus. J Virol. 2019;93(8):e02039-18. doi: 10.1128/JVI.02039-18.
29. Charbonneau J, Gendron K, Ferbeyre G, Brakier-Gingras L. The 5' UTR of HIV-1 full-length mRNA and the tat viral protein modulate the Programmed -1 ribosomal frameshift that generates HIV-1 enzymes. RNA. 2012;18(3):519-29. doi: 10.1261/rna.030346.111.
30. Park SJ, Kim YG, Park HJ. Identification of RNA pseudoknot-binding ligand that inhibits the -1 ribosomal frameshifting of SARS-coronavirus by structure-based virtual screening. J Am Chem Soc. 2011;133(26):10094-100. doi: 10.1021/ja1098325.
31. Roberts A, Deming D, Paddock C D, Cheng A, Yount B, Vogel L, Herman B D, Sheahan T, Heise M, Genrich G L, Zaki S R, Baric R, Subbarao K. A mouse-adapted SARS-coronavirus causes disease and mortality in balb/c mice. PLoS Pathog. 2007;3:e5. doi: 10.1371/journal.ppat.0030005.
32. Leber A, Bassaganya-Riera J, Tubau-Juni N, Zoccoli-Rodriguez V, Lu P, Godfrey V, Kale S, Hontecillas R. Lanthionine synthetase c-like 2 modulates immune responses to influenza virus infection. Front Immunol. 2017;8:178. doi: 10.3389/fimmu.2017.00178.

Official journal of the Spanish Society of Chemotherapy

Brief report

Revista Española de Quimioterapia
doi:10.37201/req/141.2021

Carl Llor[1,2]
Ana Moragas[3]
Josep M. Cots[4]

Implementation of the delayed antibiotic prescribing strategy. Prospective observation study in primary care

[1]University Institute in Primary Care Research Jordi Gol, Via Roma Health Centre, Barcelona, Spain
[2]Department of Public Health, General Practice. University of Southern Denmark, Odense, Denmark.
[3]Universitat Rovira i Virgili. Jaume I Health Centre, Tarragona, Spain.
[4]Primary Healthcare Centre La Marina, Barcelona, Spain.

Article history
Received: 30 September 2021; Revision Requested: 21 October 2021; Revision Received: 24 October 2021; Accepted: 26 November 2021; Published: 3 February 2022

ABSTRACT

Objectives. We aimed to compare the actual consumption of antibiotics among patients issued delayed antibiotic prescribing with the consumption observed in a non-systematic review of studies on delayed prescribing.

Methods. Observational study carried out in three primary care centres from September 2018 until March 2020. We tracked the electronic records of the 82 patients with episodes of acute bronchitis and 44 acute pharyngitis who were given a patient-led delayed prescription to determine whether the prescription was filled and when this medication was obtained.

Results. The prescriptions were never filled in 50 cases (39.7%), but five patients took another antibiotic within the first two weeks. Out of 76 patients who did take the delayed prescription, only 12 obtained the medication based on the instructions given by the doctors (15.8%).

Conclusions. The strategy of delayed antibiotic prescribing resulted in a reduction in antibiotic use, but this reduction was lower than in randomised clinical trials, being comparable to the results obtained with other observational studies on delayed antibiotic prescribing. In addition, only a few patients adhered to the doctors' instructions.

Keywords: Antimicrobial Stewardship; Primary Health Care; Antibacterial Agents.

Implementación de la estrategia de prescripción diferida de antibióticos. Estudio observacional prospectivo en atención primaria

RESUMEN

Objetivos. Evaluar el consumo de antibióticos entre los pacientes a los que se les efectuó una prescripción antibiótica diferida y compararlo con el consumo observado en una revisión no sistemática de estudios de prescripción diferida.

Métodos. Estudio observacional en tres centros de salud desde septiembre 2018 hasta marzo 2020. Se realizó un seguimiento de los registros electrónicos de los 82 pacientes con episodios de bronquitis aguda y 44 faringitis aguda a los que se les entregó una prescripción diferida para evaluar si fue a la farmacia a buscarla y cuándo la obtuvo.

Resultados. No fueron a buscar la medicación en 50 casos (39,7%), pero cinco pacientes tomaron otro antibiótico en las dos primeras semanas. De los 76 pacientes que recogieron la prescripción, solo 12 la obtuvieron según las instrucciones de sus médicos (15,8%).

Conclusiones. La estrategia de prescripción diferida reduce el consumo de antibióticos, pero esta reducción es menor que la que se observa en ensayos clínicos, siendo comparable con los resultados observados en otros estudios observacionales sobre prescripción diferida. Además, solo unos pocos pacientes siguieron las instrucciones de sus médicos.

Palabras clave: Administración de antimicrobianos; Atención Primaria; Agentes antibacterianos.

INTRODUCTION

General practitioners (GP) prescribing antibiotics for acute respiratory tract infections (RTI) are usually aware that the prescription is inappropriate but are often influenced in their decision by the perception that patients expect an antibiotic. This

Correspondence:
Carl Llor
University Institute in Primary Care Research Jordi Gol, Via Roma Health Centre, Barcelona
Gran Via de les Corts Catalanes, 497, atic - 08007 Barcelona
E-mail: carles.llor@gmail.com

conflict may also make GPs feel uncomfortable with the decision of whether to prescribe. Delayed prescribing could potentially address the patient's expectation of an antibiotic prescription, but also the GP's clinical uncertainty, while minimising actual antibiotic consumption. To put it briefly, a GP offers an antibiotic prescription, but asks the patient to wait for no spontaneous improvement before deciding whether to obtain the antibiotic at the community pharmacy. A recent individual patient data meta-analysis showed that this strategy is a safe and effective strategy for most patients, including those in higher risk subgroups and is associated with similar symptom duration as no antibiotic prescribing and is unlikely to lead to a worse symptom control than immediate antibiotic prescribing [1].

A 2017 systematic Cochrane Collaboration review, including randomised clinical trials (RCT), found that delayed antibiotic prescriptions were associated with significantly decreased antibiotic use as 31% of the cases admitted to taking the antibiotic [2]. However, the actual use of antibiotics in current practice might be higher than that reported in clinical trials. We assessed whether patients given a delayed prescription filled it or not, and if so, how many days after the index consultation was the antibiotic obtained, and we compared our results with a non-systematic review of studies on delayed antibiotic prescribing aimed at evaluating the actual consumption of antibiotics differentiating RCTs and observational studies.

METHODS

Patients were recruited from 6 general practices in three urban primary care centres in Catalonia, Spain. All the participating GPs were familiar with the delayed prescribing technique and routinely employed it in their practice. Eligible subjects were those of any age presenting with a sore throat with two Centor criteria, or uncomplicated acute bronchitis, defined as cough without chest signs in patients without lung comorbidity, as recommended by the updated version of the National Institute for Health and Clinical Excellence guideline (NICE) on RTI [3], who were visited in the different consultations from September 2018 until March 2020. We decided to stop recruiting patients at that moment because of the onset of the COVID-19 pandemic.

The recruiting doctor issued an antibiotic prescription during the consultation but advised the patient to use it after three days in the case of sore throat and after seven days for episodes of acute bronchitis and only in the absence of spontaneous improvement as suggested by the NICE guideline [3]. Patients were also given the sheet recommended by the *Plan Nacional de Resistencia a los Antibióticos* (PRAN) of the Spanish Agency of Medicines and Health Products (Supplementary material - Appendix 1). Patients were informed about their participation in a study on rationalising antibiotic treatment, but they were not aware of the real objective in an attempt not to influence their behaviour (Supplementary material - Appendix 2). Participating GPs registered whether the patients filled the prescription given and tracked the information collected in the electronic records within the first two weeks after the index consultation. In case patients collected the antibiotic they were called by the same GPs to make sure when they at-

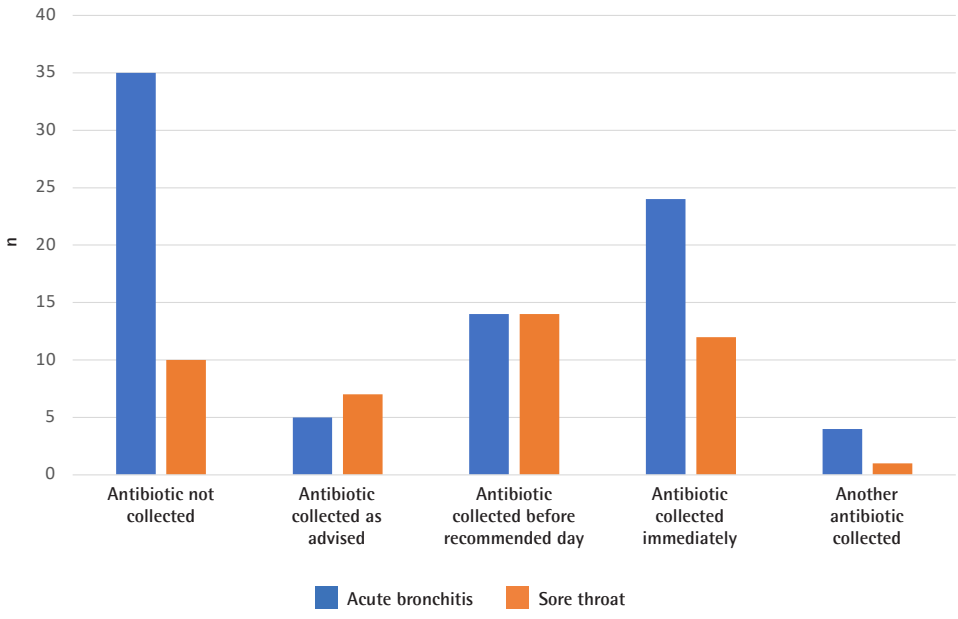


Figure 1 Distribution of patients with RTIs and their attitude about the delayed antibiotic prescribing given.

Tabla 1 **Antibiotic consumption observed with the delayed antibiotic strategy in randomised clinical trials and prospective observational studies.**

Study	Country	Setting	Sample size	Population	Condition	Number of patients who declared consuming the antibiotic (%)			Observations
						Immediate antibiotic	Delayed antibiotic	No antibiotic	
Randomised clinical trials									
Little, 1997 [4]	UK	Primary care	716	Children and adults	Sore throat	210/211 (99.5)	55/176 (31.2)	23/184 (12.5)	Collection
Dowell, 2001 [5]	UK	Primary care	191	Adults	Cough	92/92 (100)	43/95 (45.3)	-	Collection
Little, 2001 [6]	UK	Primary care	315	Children	Acute otitis media	132/151 (87.4)	36/150 (24.0)	-	Collection
Arroll, 2002 [7]	New Zealand	Primary care	129	Adults	Common cold	55/67 (85.1)	32/67 (47.8)	-	Patient led
McCormick, 2005 [8]	USA	Paediatric clinic	223	Children	Acute otitis media	109/109 (100)	38/108 (35.2)	-	Collection
Little, 2005 [9]	UK	Primary care	807	Children and adults	Lower RTI	185/193 (95.9)	39/197 (19.8)	29/182 (15.1)	Collection
Spiro, 2006 [10]	USA	Emergency department	283	Children	Acute otitis media	116/133 (87.2)	50/132 (37.9)	-	Patient led
Chao, 2008 [11]	USA	Paediatric emergency department	232	Children	Acute otitis media	-	40/106 (37.7)	13/100 (13.0)	Patient led
Little, 2014 [12]	UK	Primary care	889	Children and adults	Acute RTI	-	Recontact 34/92 (37.0); postdated 37/101 (36.6); collection 28/85 (39.2); patient-led 35/89 (39.3)	26/99 (26.3)	Recontact, postdated, collection, patient led
De La Poza, 2016 [13]	Spain	Primary care	405	Adults	Acute RTI	46/51 (90.2)	Patient-led 32/98 (32.7); collection 23/100 (23.0)	6/49 (12.2)	Patient led and collection
Mas-Dalmau, 2021 [14]	Spain	Primary care	437	Children	Acute RTI	142/148 (95.9)	37/146 (25.3)	17/142 (12.0)	Patient led
TOTAL						1,087/1,155 (94.1)	Collection 252/911 (27.7); patient-led 216/638 (33.9)	116/756 (15.3)	
Prospective observational studies									
Edwards, 2003 [15]	UK	Primary care	327	Children and adults	Acute RTI	-	136/256 (53.1)	-	Patient-led
Siegel, 2003 [16]	USA	Paediatric clinic	194	Children	Acute otitis media	NR	55/175 (31.4)	-	Collection
Marchetti, 2005 [17]	Italy	Primary care	1,672	Children	Acute otitis media	NR	383/1099 (34.8)	-	Not reported
Fischer, 2009 [18]	USA	Emergency department	144	Children	Acute otitis media	NR	105/144 (72.9)	-	Patient-led
Høye, 2011 [19]	Norway	Primary care	304	Children and adults	Acute RTIs	-	141/304 (46.4)	-	Patient-led
Francis, 2012 [20]	13 areas	Primary care	2,690	Adults	Cough or lower RTI	924/1,292 (71.5)	93/169 (55.0)	NR	Patient led
Little, 2017 [21]	UK	Primary care	28,856	Adults	Acute lower RTI	NR	NR	NR	Patient led
Moore, 2017 [22]	UK	Primary care	12,626	Adults	Sore throat	NR	115/197 (58.4)	NR	Patient led
TOTAL						924/1,292 (71.5)	Collection 55/175 (31.4); patient-led 600/1070 (56.1)	-	

Collection: collection of the prescription at the primary health centre; NR: this information is not reported in the paper; Patient-led: the patient is given the prescription the same day of the consultation; Postdated: the patient is given the prescription signed with a future date; Recontact: recontact the doctor again for a prescription; RTI: respiratory tract infection

tended the pharmacy to fill up the prescription. The study was approved by the Research Ethics Committee IDIAP Jordi Gol (reference number, 16/093).

RESULTS

A total of 126 patients were given a delayed antibiotic prescription, of which 82 cases corresponded to acute bronchitis. The mean age was 41.2 (SD 10.6) with 72 women (57.1%). The prescriptions were never obtained in 50 cases (39.7%). However, five patients admitted taking another antibiotic within the first two weeks after the index consultation. Therefore, a total of 81 patients obtained an antibiotic for that episode in the 2-week follow-up period (64.3%). Out of 76 patients who did obtain the delayed prescription, 36 declared to have filled the medication the same day of the visit (47.4%). As described in

Figure 1, only 12 patients obtained the medication based on the instructions given by the doctors (15.8%).

DISCUSSION

In this observational study of adults presenting with sore throat and acute bronchitis, the strategy of the delayed antibiotic prescribing results in a reduction in antibiotic use, but this reduction is not as high as the percentage observed in RCTs. In addition, only a small percentage of patients obtaining the medication adhered to the doctors' instructions.

Despite not asking about the actual consumption of antibiotics, 64.3% of the patients filled the delayed prescription at the pharmacy or declared taking another antibiotic. This result is not different from the actual consumption of antibiotics observed in the different studies on delayed antibiotic consumption carried out in observational studies. As shown in table 1, the actual antibiotic consumption among patients assigned to different types of delayed prescribing ranged from 19.8% to 47.8% in the different RCTs published to date [4-14] and from 31.4% to 72.9% in observational studies [15-22]. Observational studies better reflect daily practice. In RCTs of delayed prescribing GPs are usually instructed to use the approach as part of a full recommendation that includes advice about the limited effectiveness and disadvantages of using antibiotics for an infectious condition and advice about the likely time course of their symptoms and how to decide when to take the antibiotic. Symptoms of RTIs usually take longer than patients expect, and therefore advice about how long to delay the prescription is an important element of this recommendation. Inappropriate provision of advice is a possible reason for the difference in the reported consumption found in RCTs of this approach and in this study. The method of delivering the delayed prescription to the patient may also influence how delayed prescriptions are used. As shown in table 1 consumption of delayed antibiotics is lower if it is left up to the patients to collect the prescription at a later point rather than being given to the patient during the consultation. The results of our study are not dissimilar to those of observational studies using the same approach. In a study carried out in 13 European countries, in which 55% of the 169 participants, who provided data about the antibiotic consumption when a delayed antibiotic prescribing was offered, consumed an antibiotic during the study period [20]. In this study, 30% started taking their delayed antibiotics on the day that they were prescribed [20].

This study has several limitations. We cannot ensure that all the patients who filled the prescription had taken the medication, which is the most important limitation of this study. We recruited only 126 patients as the study described routine care in only a few primary care centres. Nonetheless, we do not consider that the results would have been much different if we had recruited more patients. Participants agreed to participate in a study on rationalising antibiotic therapy and this could have affected their behaviour; however, they were not informed about its real objective. Patients were not randomised; however, data on routine prescribing behaviour in everyday clinical practice can only be obtained through observational data as in our study.

Qualitative studies carried out in Spain report that some patients feel uncomfortable about being given the decision about when to use antibiotics and others report taking 'delayed' antibiotics immediately, as also suggested in our study. Some clinicians think that the strategy helps empower patients, provides reassurance, and helps to meet their expectations, but others expressed concerns about patients using them inappropriately, about masking serious illness, and about medicolegal problems [23]. Apart from giving this information sheet, GPs should be trained about the duration of delay and provide advice regarding the limited effectiveness of antibiotics, their disadvantages, and when to consider using these drugs. Otherwise, poor clinician adherence is likely to undermine the effectiveness of the strategy. Opinion leaders may be able to play a role in increasing awareness about the need for clear communication as part of any delayed prescribing strategy. It is obvious that the delayed strategy is only valid in some cases. If doctors think that an antibiotic therapy is not warranted, a delayed antibiotic strategy should not be used unless there is clear and voiced antibiotic demand for therapy by patients [24]. A 'no antibiotic strategy' is always preferable to a delayed antibiotic prescribing strategy. If delayed prescribing is offered, a clear explanation is needed about the advice to be given to patients about when to use their prescription (symptoms not resolved, not getting better, getting worse) and about safety netting (when to reconsult). If this is not voiced during the consultation, we might create confusion by sending mixed messages to patients such as 'an antibiotic is not needed, but here is an antibiotic'.

In conclusion, the strategy of delayed antibiotic prescribing is associated with a lower antibiotic consumption, but this reduction is lower than expected and only a few patients adhered to the doctors' instructions. Although this strategy could be valid in some cases doctors should prefer a no antibiotic strategy and deprescribing antibiotic courses already initiated if they no longer consider they are appropriate.

ACKNOWLEDGMENTS

To the doctors and the patients who participated in this study.

FUNDING

None to declare

CONFLICTS OF INTEREST

CL reports receiving research grants from Abbott Diagnostics. The other authors declare no competing interests.

REFERENCES

1. Stuart B, Hounkpatin H, Becque T, Yao G, Zhu S, Alonso-Coello P, et al. Delayed antibiotic prescribing for respiratory tract infections:

individual patient data meta-analysis. BMJ. 2021;373:n808. doi: 10.1136/bmj.n808.

2. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. Cochrane Database Syst Rev. 2017;9:CD004417. doi: 10.1002/14651858.CD004417.pub5.
3. National Institute for Health and Clinical Excellence. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. Clinical guideline 69, 2008 (NICE, London).
4. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonthet AL. Open randomised trial of prescribing strategies in managing sore throat. BMJ. 1997;314:722-7. doi: 10.1136/bmj.314.7082.722.
5. Dowell J, Pitkethly M, Bain J, Martin S. A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. Br J Gen Pract. 2001;51:200-5.
6. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ. 2001;322:336–42. doi: 10.1136/bmj.322.7282.336.
7. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce the use of antibiotics for the common cold? A single-blind controlled trial. J Fam Pract. 2002;51:324-8.
8. McCormick DP, Chonmaitree T, Pittman C, Saeed K, Friedman NR, Uchida T, et al. Non severe acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics. 2005;115:1455-65. doi: 10.1542/peds.2004-1665.
9. Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. JAMA. 2005;293:3029-35. doi: 10.1001/jama.293.24.3029.
10. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA. 2006;296:1235-41. doi: 10.1001/jama.296.10.1235.
11. Chao JH, Kunkov S, Reyes LB, Lichten S, Crain EF. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. Pediatrics. 2008;121:e1352-6. doi: 10.1542/peds.2007-2278.
12. Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. PIPS Investigators. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. BMJ. 2014;348:g1606. doi: 10.1136/bmj.g1606.
13. de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al. Delayed Antibiotic Prescription (DAP) Group. Prescription strategies in acute uncomplicated respiratory infections: a randomized clinical trial. JAMA Intern Med. 2016;176:21-9. doi: 10.1001/jamainternmed.2015.7088.
14. Mas-Dalmau G, Villanueva López C, Gorrotxategi Gorrotxategi P, Argüelles Prendes E, Espinazo Ramos O, Valls Duran T, et al. DAP Pediatrics Group. Delayed antibiotic prescription for children with respiratory infections: A randomized trial. Pediatrics. 2021;147:e20201323. doi: 10.1542/peds.2020-1323.
15. Edwards M, Dennison J, Sedgwick P. Patients' responses to delayed antibiotic prescription for acute upper respiratory tract infections. Br J Gen Pract. 2003;53:845–850.
16. Siegel RM, Kiely M, Bien JP, Joseph EC, Davis JB, Mendelet SG, al. Treatment of otitis media with observation and a safety-net antibiotic prescription. Pediatrics. 2003;112:527-31. doi: 10.1542/peds.112.3.527.
17. Marchetti F, Ronfani L, Nibali SC, Tamburlini G, Italian Study Group on Acute Otitis Media. Delayed prescription may reduce the use of antibiotics for acute otitis media: a prospective observational study in primary care. Arch Pediatr Adolesc Med. 2005;159:679-84. doi: 10.1097/PEC.0b013e3181b91ff0.
18. Fischer T, Singer AJ, Chale S. Observation option for acute otitis media in the emergency department. Pediatr Emerg Care. 2009;25:575-8. doi: 10.1097/PEC.0b013e3181b91ff0.
19. Høye S, Frich JC, Lindbæk M. Use and feasibility of delayed prescribing for respiratory tract infections: a questionnaire survey. BMC Fam Pract. 2011;12:34. doi: 10.1186/1471-2296-12-34.
20. Francis NA, Gillespie D, Nuttall J, Hood K, Little P, Verheij T, et al. Delayed antibiotic prescribing and associated antibiotic consumption in adults with acute cough. Br J Gen Pract. 2012;62:e639-46. doi: 10.3399/bjgp12X653561.
21. Little P, Stuart B, Smith S, Thompson MJ, Knox K, van den Bruel A, et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. BMJ. 2017;357:j2148. doi: 10.1136/bmj.j2148.
22. Moore M, Stuart B, Hobbs FDR, Butler CC, Hay AD, Campbell J, et al; on behalf of the DESCARTE investigators. Symptom response to antibiotic prescribing strategies in acute sore throat in adults: the DESCARTE prospective cohort study in UK general practice. Br J Gen Pract. 2017;67:e634-e42. doi: 10.3399/bjgp17X692321.
23. de la Poza Abad M, Mas Dalmau G, Gich Saladich I, Martínez García L, Llor C, Alonso-Coello P. Use of delayed antibiotic prescription in primary care: a cross-sectional study. BMC Fam Pract. 2019;20:45. doi: 10.1186/s12875-019-0934-7.
24. Rowe TA, Linder JA. Delayed antibiotic prescriptions in ambulatory care. Reconsidering a problematic practice. JAMA. 2020;323:1779-80. doi: 10.1001/jama.2020.2325.

Official journal of the Spanish Society of Chemotherapy

Clinical-pathological conference

Revista Española de Quimioterapia
doi:10.37201/req/138.2021

David Sánchez Fabra[1,2]
Elena Abad Villamor[3]
Susana Clemos Matamoros[1]
Juan Valle Puey[1]
María Jesús Igúzquiza Pellejero[1]
Ángel Luis García Forcada[1]

Woman with necrotising granulomatous lymphadenitis: the key was in anamnesis and physical examination

[1]Área de Medicina Interna del Hospital Reina Sofía de Tudela, Navarra, Spain.
[2]Grupo de Investigación Clínica en Enfermedades Infecciosas (G069) del Instituto de Investigación Sanitaria de Aragón. Spain.
[3]Medicina Familiar y Comunitaria del Hospital Reina Sofía de Tudela, Navarra, Spain.

Article history
Received: 25 September 2021; Revision Requested: 21 October 2021; Revision Received: 6 November 2021; Accepted: 26 November 2021; Published: 2 February 2022

CASE PRESENTATION

A 48-year-old woman was referred to the internal medicine outpatient department (OPD) due to an enlarged lymph node in her left axilla. Before the consultation, a core needle biopsy (CNB) had been performed with a pathological diagnosis of necrotizing granulomatous lymphangitis (NGL). Polymerase chain reaction (PCR) of the sample for *M. tuberculosis* complex was negative. The pathologist recommended complete excision of the lymph node to obtain more tissue for analysis. The surgeon referred the patient to internal medicine OPD before performing the procedure.

Anamnesis and examination were conducted. The patient lived in a rural area in Spain. She worked in a kindergarten and had no toxic habits. Her past medical history was unremarkable. No allergies. Regarding her family history, a grandmother had had breast cancer and a cousin had Hodgkin's lymphoma. She takes care of two dogs and six cats at home and volunteered at an animal shelter. Her pets had had ticks but she did not remember having ever had any tick bite. She had not made any trips abroad. She was on tramadol, acetaminophen, celecoxib, and omeprazole.

Current illness begins five months before the consultation, when a "lump" was noticed in the left axilla. The size of the mass has remained constant throughout this time. She did not have fever, constitutional syndrome, chills, headache, or arthromyalgia.

Physical examination: Body mass index of 40, blood pressure 129/94 mmHg, temperature 36.5ºC and heart rate 70 beats per minute. She was in good condition. No jugular ingurgitation. Cardiopulmonary auscultation and abdomen exploration were normal. A small and painless mass could be palpated at the left axilla, apparently not attached to deep layers. No other masses or enlarged lymph nodes were palpable at any other location. There were multiple cat scratches on the upper limbs (Figure 1). Examination of lower extremities was unremarkable.

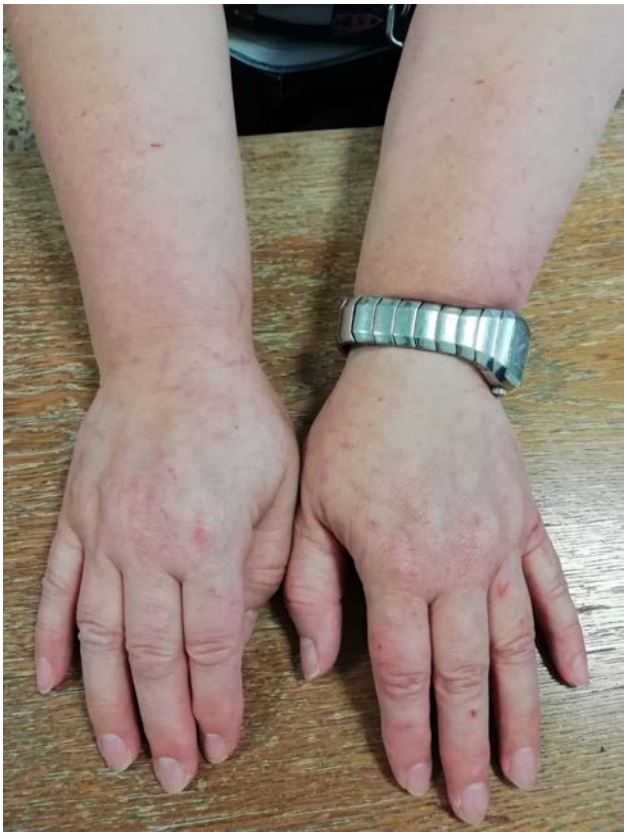


Figure 1 | **Multiple cat scratches on the upper limbs**

Correspondence
David Sánchez Fabra.
Área de Medicina Interna del Hospital Reina Sofía de Tudela, Navarra, Spain.
E-mail: davidsanchezfabra@gmail.com

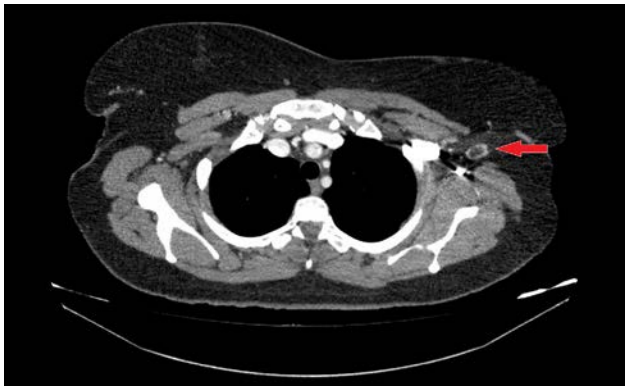


Figure 2 | **The CT scan was normal except for the already known adenopathy in axilla.**

In addition to the above-mentioned pathology data, the patient had a normal chest X-ray and mammography.

DIFFERENTIAL DIAGNOSIS

In summary, we have a patient without any type of general or infectious symptoms, with a family history of cancer and a single lymphadenopathy located in the left axilla with a pathological diagnosis that shows NGL. Regarding these data, the working diagnosis in based in two aetiologies of her condition: infectious and non-infectious.

Among the non-infectious causes it can be found sarcoidosis, a disease that can be paucisymptomatic and, although in most cases there are enlarged hiliar lymph nodes, they can also occur in extrapulmonary territories such as the axilla. Others that should be taken into account would be haematological malignancies (Hodgkin and Non-Hodgkin lymphoma), berylliosis and tumor metastases, which rarely cause necrosis [1]. It should be noted that there was a necrotizing component in the adenopathy, which would make it necessary to include Kikuchi's disease, in which adenopathies are the most frequent sign although they are usually cervical and more typical in children and young people [2], and systemic lupus erythematosus [3], but there were no other signs or symptoms leading to this diagnosis.

As for infectious causes, the differential diagnosis is broader. We could further divide infectious entities in suppurative and non-suppurative causes. Among the former are tularemia, cat scratch disease, *Yersinia pestis* and fungal infections. Regarding the non-suppurative ones, the possibility of tuberculosis, non-tuberculous mycobacteria, toxoplasmosis, leprosy, syphilis, brucellosis and some types of fungi should be considered. Some of these diseases are highly unlikely, due to the almost complete lack of symptoms and location of the lymph node. For instance, *Y. pestis* infection would affect mesenteric lymph nodes, within a general picture of severe disease; in Epstein-Barr Virus infection (EBV), enlarged lymph nodes are usually bilateral, predominantly cervical, and do not present granulomas [1].

To reach the diagnosis, the wounds on the arms and hands were crucial, what it would entail the loss of the integrity of the skin barrier. This finding reinforces the possibility of the infectious cause, and it may be due bacteria of the skin flora (bacterial adenitis due to *S. aureus*) or bacteria related to an occupational context. Let us remember that these wounds had been inflicted by cats, so the cat scratch disease, caused by *B. henselae* should be evaluated first, without forgetting other zoonoses such as those transmitted by fleas or ticks (Lyme disease, rickettsiosis, anaplasmosis, babesiosis or tularemia) [4].

PERFORMED TESTS AND CLINICAL EVOLUTION

In the OPD, it was requested a thoracoabdominal Computerized Tomography (CT) to search for other regions lymphadenopathy and a complete analysis with biochemistry, hemogram, peripheral blood morphology, proteinogram, immunoglobulins, inflammatory reactants, autoimmunity study (rheumatoid factor, Anti-nuclear Antibodies and Extractable Nuclear Antibody), Interferon-gamma release assays (IGRAs; *M. tuberculosis*) and serologies of *T. pallidum*, EBV, *T. gondii*, Cytomegalovirus, Hepatitis B and C Virus, Human Immunodeficiency Virus, *C. burnetii*, *B. henselae* and *Rickettsia* spp. The CT scan (Image 2) was normal except for the already known adenopathy in axilla. All blood studies were normal, including inflammatory reactants, except for serologies, being *Bartonella* spp. pathological, with results of: *B. Henselae* IgG, 1/4096 (pathological> 1/256); IgM, 1/80 (indicative of recent infection> 1/20). *B. quintana* IgG 1/256, IgM 1/20 (indicative of recent infection> 1/20), by indirect immunofluorescence. With a diagnosis of cat scratch disease, outpatient treatment was started with azithromycin 500 mg orally one day, followed by 250 mg orally daily for 4 more days. IgG titers for *B. henselae* were reduced by half two months later. The patient is currently asymptomatic.

DISCUSSION

To solve this case we started from a pathological diagnosis, but it was the anamnesis and examination that led us to diagnosis. We acknowledge that the order of action should have been inverse and that a PCR of *B. henselae* at the sample would have made the diagnosis.

NGL can be produced by various diseases that have been described above [1]. Granulomas are organized aggregates of macrophages and other immune cells that arise as biological structures in response to persistent (infectious or not) stimuli. Although they are defensive complexes, they can also transform into differentiated pathological structures. One of these would be necrosis, produced by macrophages. For reasons not entirely understood yet, some granulomas remain without necrosis (those caused by beryllium, sarcoidosis or Crohn's disease), while others, especially those caused by tuberculosis

and other infectious diseases (especially intracellular bacteria and fungi) do undergo it [5]. In a Danish study, 121 patients with lymphadenopathy with granulomatous inflammation in the neck and head were analysed. The most frequent diagnoses were sarcoidosis (26%), tuberculosis (22%), cat scratch disease (6%), non-tuberculous mycobacteria (7%), tumors (2%) and others (4%), with 33% of the patients without an established diagnosis. In the case of tuberculosis, the granulomas were normally necrotizing, being non-necrotizing in sarcoidosis [6]. However, a German study found that cat scratch diseases was present in 13.4% of the 454 patient with head and neck lymphadenopathy analysed, being reticular abscessed granuloma the most frequent pathological finding [7]. Diagnosis in the case of NGL can be challenging because the probability of tuberculosis is remarkable and the detection of bacilli may not be possible with conventional methods due to the low bacillary load in certain extrapulmonary territories, being necessary occasionally to confirm the diagnosis according to the response to anti-tuberculosis treatment [8,9].

Cat scratch disease is an infectious disease caused by *B. henselae*, a Gram-negative bacillus found in cats and fleas. It can be transmitted to humans through bites or scratches. The typical presentation is in children and usually presents with soft, enlarged and sometimes suppurative adenopathy, especially if there has been exposure to cats (mostly kittens, as happened in our case). One or two weeks after the inoculation wound, unilateral regional lymphadenopathies appear, which can persist for months. Other symptoms present may be malaise, arthromyalgia, anorexia, and low-grade fever. Visceral involvement has also been described, mainly hepatosplenomegaly with or without lymphadenopathy, as well as fever of unknown origin in children and occasionally meningoencephalitis, endocarditis and ocular involvement [10]. In immunosuppressed patients, *B. henselae* can cause bacillary angiomatosis, in which multisystem involvement can occur, especially skin, bone, liver and spleen [11,12].

Regarding epidemiology in Spain, seroprevalence in cats has been found in 29-78% of samples [13–15]. In humans, some studies have shown differences in seroactivity against *B. henselae*, especially considering the variable titers limit chosen to stablish exposure or infection. We could found serological evidence of *B. henselae* in 8.7-13.55% [16,17] of healthy people, being higher in occupational jobs like veterinaries (37.1%) [18].

Diagnosis is serological, because *B. henselae* is difficult to culture. Titers less than 1:64 make the diagnosis unlikely; between 1:64 and 1: 256 imply possible infection; greater than 1:256 make it very likely. IgM positivity suggests recent infection. It is important to highlight, as it happened in our case, that cross-reactivity frequently occurs in IgG titers between *B. henselae* and *B. quintana*. PCR tests can help to achieve diagnosis [10], although in our case the clinical history and the evaluation of the titers of both serologies were conclusive since, although *B. quintana* can cause trench fever and a similar clinical picture, is associated with the presence of lice and poor hygienic sanitary conditions [19].

Regarding treatment, there have been discrepancies classically in the literature about the use of antibiotics because in many cases cat scratch disease can be self-limited [10] although clinical practice guidelines recommend treatment in patients over 45 kg with 500 mg of azithromycin the first day followed by 250 mg per day for 4 more days. Patients weighing less than 45 kg (paediatrics) the dose would be 10 mg/kg the first day and 5 mg/kg the four following [20].

FINAL DIAGNOSIS

Cat scratch disease caused by *B. henselae*.

FUNDING

None to declare

CONFLICT OF INTERESTS

Authors declare no conflict of interests

REFERENCES

1. Asano S. Granulomatous lymphadenitis. J Clin Exp Hematop. 2012;52(1). doi:10.3960/jslrt.52.1
2. Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: An analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol. 1988; Nov;5(4):329-45. PMID: 3217625.
3. Kojima M, Motoori T, Asano S, Nakamura S. Histological diversity of reactive and atypical proliferative lymph node lesions in systemic lupus erythematosus patients. Pathol Res Pract. 2007;203(6). doi:10.1016/j.prp.2007.03.002
4. Brouqui P, Bacellar F, Baranton G, Birtles RJ, Bjoërsdorff A, Blanco JR, et al. Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. Clin Microbiol Infect. 2004;10(12). doi:10.1111/j.1469-0691.2004.01019.x
5. Pagán AJ, Ramakrishnan L. The Formation and Function of Granulomas. Annu Rev Immunol. 2018;36. doi:10.1146/annurev-immunol-032712-100022
6. Flyger TF, Larsen SR, Kjeldsen AD. Granulomatous inflammation in lymph nodes of the head and neck—a retrospective analysis of causes in a population with very low incidence of tuberculosis. Immunol Res. 2020;68(4). doi:10.1007/s12026-020-09144-6
7. Ridder GJ, Boedeker CC, Technau-Ihling K, Grunow R, Sander A. Role of cat-scratch disease in lymphadenopathy in the head and neck. Clin Infect Dis. 2002;35(6). doi:10.1086/342058
8. Chakravorty S, Sen MK, Tyagi JS. Diagnosis of extrapulmonary tuberculosis by smear, culture, and PCR using universal sample processing technology. J Clin Microbiol. 2005;43(9). doi:10.1128/JCM.43.9.4357-4362.2005
9. Alves F, Baptista A, Brito H, Mendonça I. Necrotising granulomatous lymphadenitis. BMJ Case Rep. Published online 2011. doi:10.1136/bcr.11.2010.3548

10. Klotz SA, Ianas V, Elliott SP. Cat-scratch Disease. Am Fam Physician. 2011. Jan 15;83(2): 152-5. PMID 21243990

11. Zangwill KM. Cat Scratch Disease and Bartonellaceae. Pediatr Infect Dis J. 2021;40(5S). doi:10.1097/inf.0000000000002776

12. Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, et al. Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997–2015). Eur J Clin Microbiol Infect Dis. 2021 Apr;40(4):849-857. doi: 10.1007/s10096-020-04087-0.

13. Gracia MJ, Marcén JM, Pinal R, Calvete C, Rodes D. Prevalence of *Rickettsia* and *Bartonella* species in Spanish cats and their fleas. J Vector Ecol. 2015 Dec;40(2):233-9. doi: 10.1111/jvec.12159.

14. Pons I, Sanfeliu I, Quesada M, Anton E, Sampere M, Font B, et al. Prevalence of Bartonella henselae in cats in Catalonia, Spain. Am J Trop Med Hyg. 2005 Apr;72(4):453-7. PMID: 15827285.

15. Álvarez-Fernández A, Baxarias M, Prandi D, Breitschwerdt EB, Solano-Gallego L. Bartonella henselae antibodies in serum and oral fluid specimens from cats. Pathogens. 2021 Mar 11;10(3):329. doi: 10.3390/pathogens10030329.

16. Santibáñez S, Caruz A, Márquez-Constán J, Portillo A, Oteo JA, Márquez FJ. Serologic study of Bartonella sp. infection among human population of Southern Spain. Enferm Infecc Microbiol Clin (Engl Ed). 2020 Dec 14:S0213-005X(20)30399-2. doi: 10.1016/j.eimc.2020.10.020.

17. Pons I, Sanfeliu I, Cardeñosa N, Nogueras MM, Font B, Segura F. Serological evidence of Bartonella henselae infection in healthy people in Catalonia, Spain. Epidemiol Infect. 2008 Dec;136(12):1712-6. doi: 10.1017/S0950268808000368.

18. Portillo A, Maggi R, Oteo JA, Bradley J, García álvarez L, San martín M, et al. Bartonella spp. Prevalence (serology, culture, and PCR) in sanitary workers in La Rioja Spain. Pathogens. 2020 Mar 4;9(3):189. doi: 10.3390/pathogens9030189.

19. Foucault C, Brouqui P, Raoult D. *Bartonella quintana* characteristics and clinical management. Emerg Infect Dis. 2006;12(2). doi:10.3201/eid1202.050874

20. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59(2). doi:10.1093/cid/ciu296

Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

Revista Española de Quimioterapia
doi:10.37201/req/112.2021

Beatriz González-Rodríguez[1]
María González-Rodríguez[2]
Natalia Bejarano Ramírez[3,4]
Francisco Javier Redondo Calvo[4,5,6]

Optic neuritis as sign presentation of acute disseminated encephalomyelitis following *Mycoplasma pneumoniae* infection

[1]Ophthalmologist, Virgen de la Salud Hospital, Toledo, Spain.
[2]Pharmacologist. IDIS (Sanitary Investigation Institute of Santiago), the NEIRID Lab (Neuroendocrine Interactions in Rheumatology and Inflammatory Diseases) Research Laboratory 9, Santiago University Clinical Hospital, Santiago de Compostela, A Coruña, Spain.
[3]Department of Paediatrics, University General Hospital, Ciudad Real, Spain.
[4]Faculty of Medicine, Ciudad Real, Spain.
[5]Department of Anaesthesiology and Critical Care Medicine. University General Hospital, Ciudad Real, Spain.
[6]Head of Research. University General Hospital, Ciudad Real, Spain.

Article history
Received: 8 August 2021; Revision Requested: 21 September 2021; Revision Received: 6 November 2021; Accepted: 11 November 2021; Published: 25 February 2022

Sir,

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disorder of the central nervous system (CNS) affecting the white matter of brain and spinal cord [1,2]. Rapid onset encephalopathy associated with neurological deficits preceded by a prodromal phase (fever, nausea, headache) is the most common presentation. Neurologic features depend on the location of lesions: pyramidal signs, hemiplegia, ataxia, cranial nerve palsies, visual loss due to optic neuritis, seizures, spinal cord involvement, aphasia, coma. Optic neuritis (ON) represents a 7-23% of cases [1,3–6], so it is not the most common form of presentation. Lesions in ADEM are multiple and asymmetric, affecting subcortical and central white matter and cortical gray-white junction. Gray matter of thalami and basal ganglia are also involved [1]. Diagnosis is made based on clinical and radiological findings. Magnetic Resonance Imaging (MRI) results can be classified in 4 types: a) Small lesions, b) Large, tumefactive lesions c) Symmetric bithalamic affection, d) Acute hemorrhagic encephalomyelitis. Spinal cord involvement is reported to represent 11-28%, typically in the thoracic region [1]. Differential diagnosis is challenging, and multiple sclerosis should be considered [1,2]. Steroids, intravenous immunoglobulin and plasma exchange are the main used treatments. Here we describe a case of ADEM with ophthalmologic debut and discuss its main clinical aspects.

16-year-old female presented to our clinic complaining of blurry vision and ocular pain that started a week ago concurring with flu-like symptoms and fever. Ophthalmic examination showed up right optic nerve edema (Figure 1), confirmed with optic coherence tomography (Figure 2) that revealed thickening of retinal fiber nerve layer in the right eye. Right eye chromatic vision was altered and she had a concentric visual field reduction. Brain computed tomography (CT) was normal, and cerebrospinal fluid analysis showed pleocytosis and increased protein concentration. She received intravenous megadoses of methylprednisolone, but after 24h she experienced worsening of her symptoms: pain, strength loss in her low extremities and walking difficulties. Serology studies were negative, except *Mycoplasma pneumoniae* IgM. Oligoclonal bands, anti-myelin oligodendrocyte glycoprotein antibodies (MOG-abs), anti-aquaporin 4 antibodies, all tested negative. MRI neuroimaging demonstrated thickening of right optic nerve, small supra and infratentorial demyelinating lesions and large dorsal myelitis, all of these suggested ADEM. We started plasmapheresis with excellent response, showing improvement in optic disc swelling, visual field defect and strength loss, although she needed physical rehabilitation. She followed treatment with low descendent dose of oral steroids to avoid further relapses.

ADEM is usually seen in prepuberal patients preceded by a viral infection or post vaccination [1,2], and less frequently post-bacterial infection caused by *Mycoplasma*, *Chlamydia*, *Legionella*, *Campylobacter* and *Streptococcus* [7], but main causes are measles, rubella and chickenpox [8]. It is unclear whether central nervous system affection is due to direct *Mycoplasma pneumoniae* infection or antibodies produced against this pathogen cross-react with myelin antigens [7]. Extrapulmonary complications of this infection include encephalitis, optic neuritis, psychosis, stroke, cranial nerve palsies, aseptic meningitis and it can trigger immune mediated neurological diseases such as ADEM, Guillain-Barré syndrome and transverse myelitis [9,10]. Encephalitis is common in children, and up to a 20% of patients do not have respiratory compromise, as in our case [10]. Diagnosis can be made with PCR (gold standard) or serology (IgM for *Mycoplasma pneumoniae).* It is an important differential diagnosis in demyelinating diseases in prepuberal patients. Antibiotic treatment in controversial, it was not used in our case [8]. Visual prognosis in optic neuritis due to ADEM is good when it is diagnosed early and treated aggressively [3].

Correspondence:
Beatriz González-Rodríguez
Virgen de la Salud Hospital, Toledo. Barber Avenue, 30. Zip Code 45004, Toledo, Castilla La Mancha, Spain.
E.mail: dragonzalezrodriguez@outlook.es

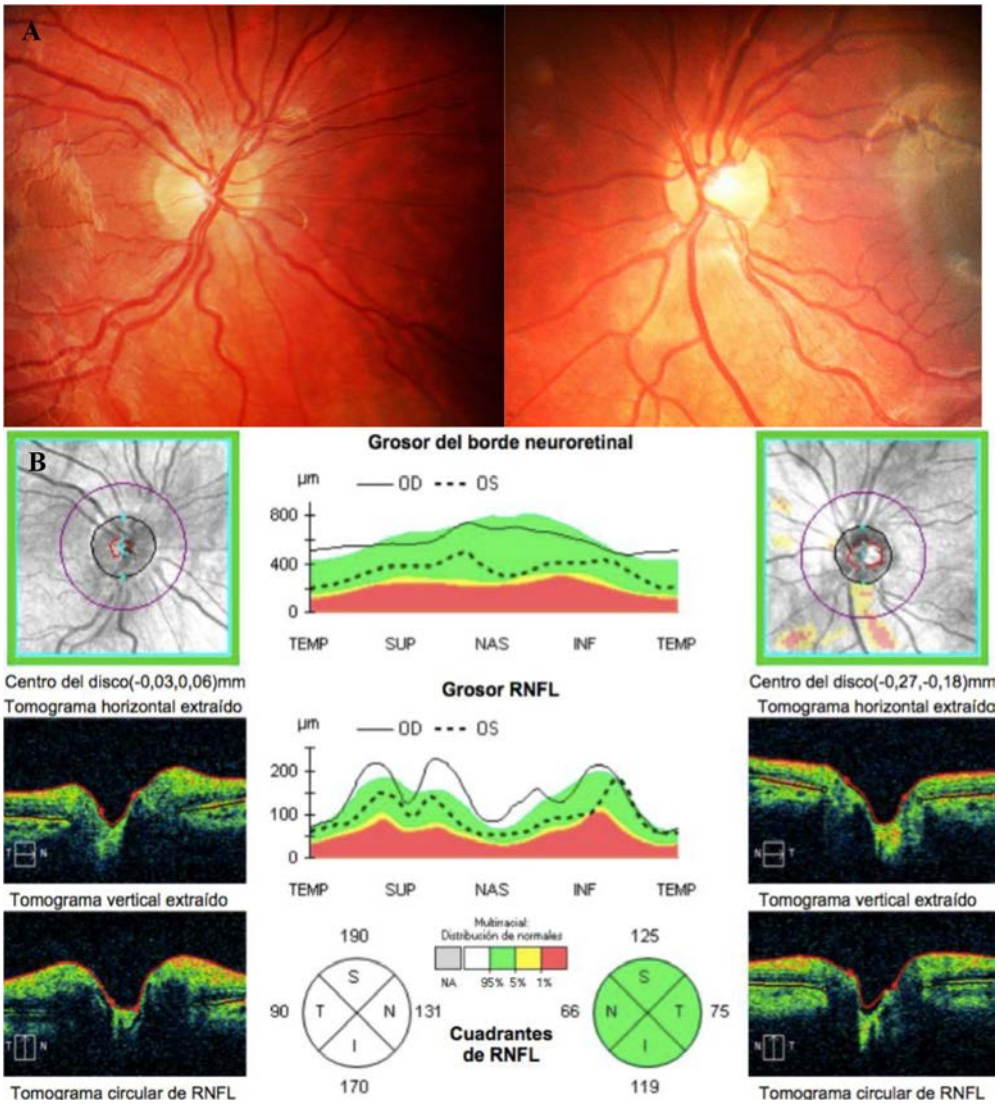


Figure 1 | **Optic nerve images showing swelling of the right optic nerve (left image) and absence of abnormalities in the left one (right image). B) Optical coherence tomography (OCT) images confirmed optic disc swelling of the right eye (left side of the image), there is a thickness augmentation of retinal nerve fiber layer (RNFL) as shown above.**

Pediatric ADEM belongs to a group of disorders characterized by acute or subacute onset of neurological deficits with inflammatory demyelination of CNS. One of the clinical subgroups is ADEM-optic neuritis. Inflammatory optic neuritis is a frequent cause of acute visual loss in young adults, although visual prognosis is excellent in most cases, many patients develop demyelinating lesions during its evolution. ON was described as a form of relapsing course of the disease, with one or more episodes of ON [5], but as a form of presentation, preceding ADEM, it is infrequent [1,7]. Manifestations of optic nerve inflammation include vision loss, pain with ocular movements, dyschromatopsia, optic nerve swelling, relative pupillary afferent defect and central visual field loss; it is usually unilateral, although bilateral cases have been reported. ADEM-ON has been classified as an entity within "MOG-spectrum disorder". MOG-abs positivity is common in children with optic nerve affection, since MOG is a glycoprotein that is only present in the CNS, it maintains myelin sheath integrity. Their positivity supports the diagnosis; these antibodies have also been related to the risk of new events [5]. Particularities of our case are that ON preceded ADEM, time between both events was 24h and MOG-abs resulted negative. This case has the aim to contribute to a better description of presentation and epidemiology of *Mycoplasma pneumoniae* as a trigger of demyeli-

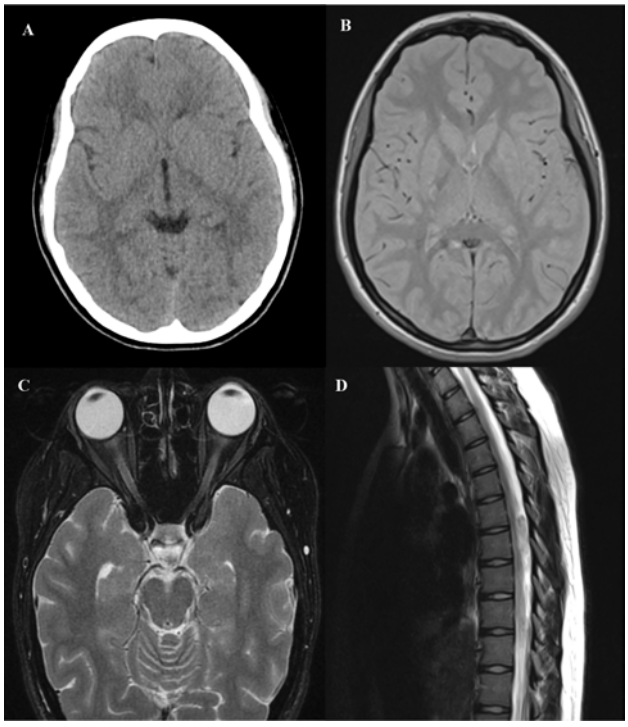


Figure 2 | **A) Normal CT brain scan. B) Brain MRI showing features of acute disseminated encephalomyelitis with small lesions. C) Orbit MRI demonstrating unspecific inflammatory changes in the right optic nerve, congruent with optic neuritis. D) Spine MRI suggestive of dorsal myelitis.**

nating diseases, and remark the uncommon ophthalmological debut of ADEM with optic neuritis.

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Tenembaum SN. Acute disseminated encephalomyelitis. Handb Clin Neurol. 2013;112:1253-62. DOI: 10.1016/b978-0-444-52910-7.00048-9
2. Paolilo RB, Deiva K, Neuteboom R, Rostásy K, Lim M. Acute Disseminated Encephalomyelitis: Current Perspectives. Children (Basel). 2020 Nov 3;7(11):210. DOI: 10.3390/children7110210
3. Mendonca N, Shah AJ, Saldanha M, Gonsalves SR. Acute disseminated encephalomyelitis presenting as optic neuritis in a case of idiopathic thrombocytopaenic purpura. BMJ Case Rep. 2014;2014:bcr2014204631. DOI: 10.1136/bcr-2014-204631
4. Huppke P, Rostasy K, Karenfort M, Huppke B, Seidl R, Leiz S, et al. Acute disseminated encephalomyelitis followed by recurrent or monophasic optic neuritis in pediatric patients. Mult Scler. 2013;19(7):941-6. DOI: 10.1177/1352458512466317
5. Serra M, Presicci A, Fucci M, Margari M, Palumbi R, Peschechera A, et al. Acute Disseminated Encephalomyelitis followed by Optic Neuritis: A Rare Syndrome of Uncertain Treatment and Prognosis. Neuropediatrics. 2020;51(4):286-91. DOI: 10.1055/s-0039-3402004
6. Chan WH, Lloyd IC, Ashworth JL, Jain S, May K, Hughes I, et al. Acute disseminated encephalomyelitis associated with optic neuritis and marked peri-papillary hemorrhages. Eye (Lond). 2011;25(12):1658-9. DOI: 10.1038/eye.2011.227
7. Laila A, El-Lababidi RM, Hisham M, Mooty M. A case of acute disseminated encephalomyelitis following *Mycoplasma pneumoniae* infection. IDCases. 2018;12:41-3. DOI: 10.1016/j.idcr.2018.03.003
8. Molero-Senosiain M, Domingo-Gordo B, Fernández Cabrera C, Hernández-García E, Gómez de Liaño R. Neuro-ophthalmological manifestations as complication of an infection with *Mycoplasma pneumoniae* and subsequent development of disseminated acute encephalitis. Arch Soc Esp Oftalmol. 2020 May;95(5):254–8. DOI: 10.1016/j.oftale.2020.01.012
9. Yimenicioğlu S, Yakut A, Ekici A, Bora Carman K, Cagrı Dinleyici E. *Mycoplasma pneumoniae* infection with neurologic complications. Iran J Pediatr. 2014;24(5):647-51. PMID: 25793076
10. Cadario ME, Ellis A, Garea M, Cairnie A, Mistchenko A, García Roig C, et al. Acute disseminated encephalomyelitis due to *Mycoplasma pneumoniae* in a previously healthy boy. Rev Argent Microbiol. 2019;51(2):153-6. DOI: 10.1016/j.ram.2018.06.003

Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/136.2021

Maximilien Neukirch[1]
Rocío Sánchez-Ruiz[1]
José María Navarro-Marí[2]
José Gutiérrez-Fernández[2,3]

Infección/colonización del tracto genital femenino por *Streptococcus pneumoniae* en paciente con esterilidad primaria

[1]Unidad de Gestión Clínica de Obstetricia y Ginecología, Sección de Reproducción Humana. Hospital Universitario Virgen de las Nieves- Instituto de Investigación Biosanitaria de Granada.
[2]Servicio de Microbiología, Hospital Universitario Virgen de las Nieves- Instituto de Investigación Biosanitaria de Granada.
[3]Departamento de Microbiología, Facultad de Medicina, Universidad de Granada- Instituto de Investigación Biosanitaria de Granada.

Article history
Received: 21 September 2021; Revision Requested: 5 October 2021; Revision Received: 5 November 2021; Accepted: 26 November 2021; Published: 7 February 2022

Estimado Editor:

Entre los muchos factores que interfieren en la fertilidad se encuentran las infecciones del tracto genital, no sólo como etiología del factor tubárico, sino también por su influencia en el factor vaginal, cervical, uterino y peritoneal. Infecciones por *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum* y VIH son las más relevantes en cuanto a esterilidad, pero queda menos claro el rol que desempeñan otros microorganismos [1,2]. En las cervicitis se reduce la posibilidad de concepción espontánea [3] pero se considera al factor cervical una causa inusual de esterilidad y soslayan su importancia mediante "inseminación uterina" o "fecundación in-vitro" (FIV) También se ha demostrado una reducción en la tasa de recién nacido vivo mediante FIV en los casos con sangre en el catéter de transferencia embrionaria por una cervicitis clínica inadvertida [4]. *Streptococcus pneumoniae* coloniza el tracto respiratorio superior y de forma transitoria puede formar parte de la microbiota comensal del tracto genital femenino, pudiendo producir en raros casos infecciones cervicales y pélvicas, especialmente si existen factores predisponentes [5].

En este trabajo se presenta el caso de una pareja que consulta por esterilidad primaria de dos años de evolución con aislamiento de *S. pneumoniae* y que desaparece tras el tratamiento con antibióticos.

Mujer de 31 años sin antecedentes médicos de interés. Niega hábitos tóxicos. Recientemente había consultado por sangrado intermenstrual y coitorragia de larga evolución. Se realizó colposcopia que ponía de manifiesto la presencia de importante ectopia cervical con vascularización típica. Se efectuaron biopsias cervicales que informaban de denso infiltrado inflamatorio sugerente de cervicitis, negativas para el virus del papiloma humano. La paciente no realizó tratamiento alguno tras este diagnóstico y se inició estudio de esterilidad, evidenciándose obstrucción tubárica unilateral derecha, con seminograma del varón normal, por lo que se indicó FIV. Al realizar transferencia se objetiva cérvix hiperémico y friable al roce, así como abundante leucorrea inespecífica. La embriotransferencia transcurre sin incidencias reseñables y a los 14 días se realiza determinación de B-hcG sérica con resultado negativo. Tras finalizar esta primera FIV se reevalúa a la paciente, objetivando persistencia de clínica cervical, por lo que se procede a estudios microbiológicos de exudados vaginal y endocervical según protocolos [6]. Sólo se encontró que, tras 24 horas de incubación en CO_2, crecieron abundantes colonias en cultivo puro en el medio de agar sangre (Becton-Dickinson, España) y agar chocolate (Becton-Dickinson) que se identificaron correctamente mediante MALDI-TOF (Bruker Biotyper, Billerica, MA, USA), con un score 2,103, como *S. pneumoniae*, sensible a optoquina (BD BBL, España) en disco. Los estudios de PCR para *C. trachomatis*, *N. gonorrhoeae*, *Mycoplasma* spp., *Ureaplasma* spp. y virus del herpes simple (BD Max, Becton-Dickinson Diagnostics, Sparks, MD, EE. UU.) fueron negativos. El estudio de sensibilidad antibiótica se realizó mediante E-test (EUCAST 2020) con los siguientes valores de CMI (mg/L) interpretados como sensibles para linezolid (1,5), moxifloxacino (0,125), meropenem (0,04), penicilina (<0,016), cefotaxima (0,016), cotrimoxazol (0,38), vancomicina (0,75), y eritromicina y clindamicina (0,25); e intermedio para levofloxacino (0,5). Tras tratamiento con clindamicina en óvulos (100 mg/24h) durante 3 días y posteriormente eritromicina oral 2 g/24 horas durante otros 3 días, con probióticos por criterio clínico, la paciente refiere mejoría clínica, con desaparición de la coitorragia y el sangrado intermenstrual. La exploración manifestó ausencia de leucorrea y sangrado, y disminución de la eritroplasia. El estudio microbiológico repetido fue negativo. Se realizó un segundo ciclo de FIV. Durante la transferencia embrionaria ni hubo sangrado ni dificultad para el procedimiento. El resultado de la BhcG a los 14 días tras transferencia fue de 214 mUI/ml. A las 6 semanas de gestación se realizó ecografía transvaginal en la que se consta-

Correspondencia:
José Gutiérrez-Fernández.
Servicio de Microbiología. Hospital Universitario Virgen de las Nieves.
Avenida de las Fuerzas Armadas, 2. E-18012 Granada, España.
josegf@go.ugr.es

ta la presencia de un embrión con actividad cardíaca positiva, confirmándose transferencia embrionaria exitosa y gestación clínica evolutiva.

S. pneumoniae no forma parte de la microbiota vaginal habitual y su aislamiento en exudados vaginal/cervical se da en menos del 1% de las mujeres [5]. Sin embargo, *S. pneumoniae* puede acceder a la mucosa vaginal por contaminación de las manos o por práctica sexual orogenital o vía hematógena, como se ha descrito con otras especies [7]. Entre los factores de riesgo para colonización del tracto genital se encuentran el uso de dispositivos intrauterinos, periodo posparto o posaborto o cirugía ginecológica reciente [8]. Ninguna de estas circunstancias concurría en el caso expuesto. Consideramos que la cervicitis provocada por este microorganismo podría estar contribuyendo a un descenso en la fertilidad natural de la pareja, así como a un fracaso tras transferencia embrionaria. Se desconoce la patogenia de la obstrucción tubárica de la paciente, que no reconocía haber padecido previamente ningún episodio clínico compatible con enfermedad pélvica inflamatoria. Además, desconocemos si estaba vacunada frente al neumococo, aunque manifestó haber realizado correctamente la vacunación durante su etapa infantil. Sin embargo, dada la edad de la paciente en el momento del estudio y al no estar incluida en ningún grupo de riesgo, lo más probable es que no estuviese vacunada dado que esta vacuna se incluyó en calendario vacunal universal bastante más tarde. Finalmente, no se han publicados episodios de aislamientos de neumococo en exudado cervical de pacientes estériles, ni evidencias que lo justifiquen.

En conclusión, los estudios microbiológicos del aparato genital deberían ser amplios, no limitándose a poblaciones de riesgo y empleando pruebas que permitan la detección de patógenos estrictos y oportunistas, ya que de forma indirecta se reduce el riesgo de infertilidad de origen infeccioso. Además, permitiría también disminuir el uso de tratamiento empíricos amplios y resolver situaciones clínicas complejas.

FINANCIACIÓN

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

BIBLIOGRAFÍA

1. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018; 62:2-10. doi: 10.1016/j.clinbiochem.2018.03.012.
2. Moragianni D, Dryllis G, Andromidas P, Kapeta-Korkouli R, Kouskouni E, Pessach I, Papalexis P, Kodonaki A, Athanasiou N, Pouliakis A, Baka S. Genital tract infection and associated factors affect the reproductive outcome in fertile females and females undergoing *in vitro* fertilization. Biomed Rep. 2019; 10:231-237. doi: 10.3892/br.2019.1194.
3. Estudio y tratamiento de la esterilidad de origen uterino. Guía de Asistencia práctica. Prog Obstet Ginecol 2019; 62:497-510. doi: 10.20960/j.pog.00238.
4. Espinós JJ, Fabregues F, Fontes J, García-Velasco JA, Llácer J, Requena A, Checa MÁ, Bellver J; Spanish Infertility SWOT Group (SISG). Impact of chronic endometritis in infertility: a SWOT analysis. Reprod Biomed Online. 2021; 42:939-951. doi: 10.1016/j.rbmo.2021.02.003.
5. Sallam A, Paes B. *Streptococcus pneumoniae*: an old bug with significant maternal-newborn implications. Am J Perinatol. 2004; 21:491-495. doi: 10.1055/s-2004-835967.
6. Carrillo-Ávila JA, Serrano-García ML, Fernández-Parra J, Sorlózano-Puerto A, Navarro-Marí JM, Stensvold CR. Gutiérrez-Fernández J. Prevalence and genetic diversity of *Trichomonas vaginalis* in the general population of Granada and co-infections with *Gardnerella vaginalis* and *Candida* species. J Med Microbiol. 2017; 66:1436-1442. doi :10.1099/jmm.0.000603.
7. Mora-Palma JC, Guillot-Suay V, Sánchez-Gila MM, Gutiérrez-Fernández J. Pelvic inflammatory disease by *Streptococcus constellatus*. Clinical experience and a review. Rev Esp Quimioter. 2020; 33:285-288. doi:10.37201/req/020.2020.
8. Garrido-Jareño M, Monzó-Fabuel S, Gil-Brusola A, Acosta-Boga B. Enfermedad pélvica inflamatoria por *Streptococcus pneumoniae*. Enferm Infecc Microbiol Clin. 2018; 36:252–253. doi:1016/j.eimc.2017.07.004.

Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/137.2021

María Nieves Carmona Tello[1]
Laura Suárez Hormiga[2]
Margarita Bolaños Rivero[1]
Isabel de Miguel Martínez[1]

Endocarditis por *Kingella kingae* en un paciente adulto

[1]Servicio de Microbiología y Parasitología Clínica, Hospital Universitario Insular de Gran Canaria.
[2]Unidad de Enfermedades Infecciosas y Medicina Tropical, Hospital Universitario Insular de Gran Canaria.

Article history
Received: 22 September 2021; Accepted: 26 November 2021; Published: 9 February 2022

Estimado Editor:

Kingella kingae es un cocobacilo gramnegativo, beta-hemolítico, de crecimiento lento y cultivo exigente que pertenece al grupo HACEK (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella* y *Kingella*). Forma parte de la microbiota orofaríngea, fundamentalmente en niños y se transmite de persona a persona por contacto directo [1-3].

En niños o pacientes inmunocomprometidos, se asocia especialmente a artritis séptica y bacteriemias, que normalmente cursan de forma benigna. La endocarditis infecciosa puede observarse a cualquier edad afectando tanto a válvulas nativas como protésicas [4].

Presentamos el caso de un paciente de 43 años con Síndrome de Marfan e insuficiencia renal crónica en estadío 3A debido a nefropatía por IgA, en tratamiento con inmunosupresores. En 2004 se interviene para la sustitución de la aorta ascendente y la válvula aórtica (Cirugía de Bentall modificado) y la reintervención para corrección de pseudoaneurisma aórtico con mediastinitis. Es portador de marcapasos definitivo por bloqueo post-quirúrgico, que precisa recambio también en 2004 por endocarditis infecciosa con cultivo negativo, e implante de dispositivo en lado contralateral.

Su hija de 18 meses asiste a guardería.

En 2020 acude al hospital por fiebre persistente de más de 39ºC, náuseas y vómitos postpandriales de 24 horas de evolución. No refiere tos, expectoración, diarrea ni síndrome miccional, apreciándose buen aspecto del bolsillo del marcapasos. Seis semanas antes, se somete a recambio de pila del marcapasos.

La analítica sanguínea al ingreso presenta: 8,500 leucocitos/µL, proteína C reactiva 11,72 mg/dL y procalcitonina 7,72 ng/mL. El diagnóstico de sospecha de endocarditis se confirma con una ecocardiografía transesofágica (ETE) que indica insuficiencia aórtica periprotésica leve posterior con imagen móvil en porción auricular alta de 9 x 3 mm, sugestiva de vegetación y electrodo de marcapasos normosituado, sin imágenes

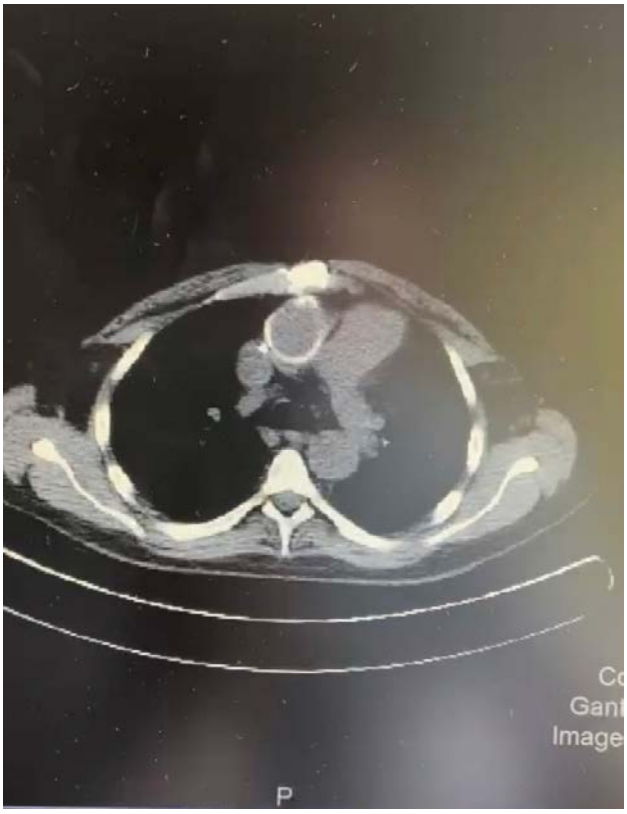


Figura 1 | **PET-TC donde se observa captación persistente en anillo valvular y endoprótesis, indicativa de proceso infeccioso compatible con endocarditis.**

Correspondencia:
Margarita Bolaños Rivero.
Servicio de Microbiología y Parasitología Clínica,
Hospital Universitario Insular de Gran Canaria.
Avda. Marítima del Sur, s/n, 35016, Gran Canaria, España.
Tfno: 928441763 - Fax: 928441861
E-mail: mbolriv@gobiernodecanarias.org

patológicas en válvulas nativas, prótesis aórtica ni tubo de dacron. Tras la extracción del primer par de hemocultivos, se inicia antibioterapia empírica con daptomicina y ceftazidima.

Pasadas 24 horas, se extrae el segundo par de hemocultivos. Ambos pares se procesan mediante el sistema BacT/ALERT® 3D (Biomerieux®), resultando positivos en 17 y 15 horas, respectivamente. En la tinción de Gram se observan cocobacilos gramnegativos y en el subcultivo, el crecimiento de colonias cremosas y brillantes en agar sangre y agar chocolate, que se identifican como *K. kingae* por espectrometría de masas (MALDI- TOF MS [Bruker®]).

La sensibilidad antimicrobiana se efectúa mediante prueba de epsilometría (E-test, Biomerieux®) en agar chocolate con suspensión 0,5 de McFarland resultando sensible (según los criterios del European Committee on Antimicrobial Susceptibility Testing [EUCAST]) a ampicilina (CMI = 0,03 mg/L), cefotaxima (CMI = 0,064 mg/L), meropenem (CMI = 0,012 mg/L), ciprofloxacino (CMI = 0,023 mg/L), levofloxacino (CMI = 0,032 mg/L), claritromicina (CMI = 0,75 mg/L), azitromicina (CMI = 0,25 mg/L), rifampicina (CMI = 0,38 mg/L) y tetraciclina (CMI = 0,125 mg/L).

Se confirma el diagnóstico de endocarditis infecciosa sobre electrodo del marcapasos y tubo valvulado de prótesis aórtica por *K. kingae*, ajustándose el tratamiento a ceftriaxona.

Tras tratamiento antimicrobiano dirigido, se consigue estabilización clínica, analítica y negativización de posteriores hemocultivos. A los doce días se realiza una tomografía por emisión de positrones (PET), con resultados compatibles con endocarditis infecciosa activa en válvula aórtica, tubo de recambio en aorta ascendente y captación patológica en extremo distal del cable de marcapasos, probablemente relacionado con una vegetación (Figura 1).

A los 18 días del comienzo, la ETE sugiere vegetaciones de 9 x 3 mm en zona auricular alta y de 6 x 3 mm adheridas al cable del marcapasos engrosado, cercano a válvula tricúspide.

A los 40 días del ingreso, se realiza un segundo PET, donde se observa captación persistente indicativa de proceso infeccioso en anillo valvular y endoprótesis.

Se presenta el caso en el Comité de Endocarditis, decidiéndose no intervenir de entrada por el alto riesgo quirúrgico del paciente.

El tratamiento antibiótico se completa con ceftriaxona durante 6 semanas.

Tras 8 meses de seguimiento estrecho, el paciente sigue confirmando ausencia de fiebre o febrícula, disnea u otra sintomatología. En los 5 posteriores análisis seriados realizados hasta la fecha, los hemocultivos fueron negativos y los reactantes de fase aguda han permanecido dentro del rango de normalidad. En las siguientes ecocardiografías transesofágicas, se observan vegetaciones de menor tamaño en el electrodo (máximo 7 mm) sin afectación protésica ni de otras válvulas. La persistencia de estas vegetaciones en un paciente sin tratamiento antibiótico supresor, con hemocultivos negativos y completamente asintomático, puede sugerir que son vegetaciones estériles.

El caso descrito, es una entidad rara en adultos y presenta una gran morbimortalidad [5,6]. El crecimiento del microorganismo exigente y la evolución clínica subaguda, influye en el debut habitual con grandes vegetaciones en válvulas, que normalmente, suelen responder a tratamiento médico [7,8].

FINANCIACIÓN

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

BIBLIOGRAFÍA

1. Rodríguez-Bouza H, De La Fuente-Aguado J, Rubianes-Gonzalez M, Crespo-Casal Sopeña-Pérez-Argüelles B. Endocarditis por *Kingella kingae*. An Med Inter 2001; 18: 659- 60.
2. Adebiyi EO, Ayoade F. *Kingella Kingae*. StatPearls Publishing 2021; ID: NBK547690 PMID: 31613470.
3. Guarch-Ibáñez B, Cabacas A, González-López JJ, García-González MM, Mora C, Villalobos P. Primer brote documentado de artritis séptica por *Kingella kingae* en una guardería de España. Enferm Infecc Microbiol 2020; doi: 10.1016/j.eimc.2020.11.006.
4. Yagupsky P. *Kingella kingae*: carriage, transmission, and disease. Clin Microbiol Rev 2015; 28: 54–79. doi:10.1128/CMR.00028-14.
5. Odum L, Jensen KT, Slotsbjerg TD. Endocarditis due to *Kingella kingae*. Eur Clin Microbiol 1984; 3: 263–6. doi:10.1007/BF02014899.
6. Holmes AA, Hung T, Human DG, Campbell AIM. *Kingella kingae* endocarditis: A rare case of mitral valve perforation. Ann Pediatric Cardiol 2011; 4(2): 210-2. doi: 10.4103/0974-2069.84664.
7. Mustafa-Hellou M, Sagi N, Ofran Y, Geffen Y, Ghanem-Zoubi N. Endovascular Infection with *Kingella kingae* Complicated by Septic Arthritis in Inmunocompromised Adult Patient Emerg Infect Dis 2020; 26: 2999-3001. doi: 10.3201/eid2612.191665.
8. Martínez-Olorón P, Romero-Ibarra C, Torroba-Álvarez L, Pérez-Ocón A. Endocarditis por *Kingella kingae*. An Pediatr 2011; 74: 274-88. doi: 10.1016/j.anpedi.2010.10.01.

Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

Revista Española de Quimioterapia
doi:10.37201/req/147.2021

Successful management of remdesivir extravasation

David Conde-Estévez[1,2]
Melisa Barrantes-González[3]
Maria Renne Cotrina Soliz[4]
Santiago Grau[1,3]

[1]Infectious Disease Control. Department of Pharmacy. Hospital Universitari del Mar. Passeig Marítim 25–29, E-08003, Barcelona, Spain
[2]Hospital del Mar Medical Research Institute (IMIM), Hospital Universitari del Mar, Barcelona, Spain
[3]Hospital Clínic, Barcelona, Spain
[4]Hospital Universitari del Mar., Barcelona, Spain

Article history
Received: 10 October 2021; Accepted: 26 November 2021; Published: 4 February 2022

Sir,

Extravasation is a potentially severe complication of treatments by intravenous administration. Their consequences may include tissue necrosis, compartment syndrome, infection, ulceration, and partial or total loss of limb function [1, 2]. Information about extravasation management is scarce and often limited to case reports. Primarily, **it was described remdesivir as a vesicant drug due to formation of blisters, hemorrhage, and localized edema when extravasated [3]. Recently three cases of remdesivir extravasation were described, two of them treated with hyaluronidase injections [4]. However suitable early management of remdesivir extravasation remains unknown. Here,** a successful management case of remdesivir extravasation with only dry heat is first described.

A 68-year-old woman was admitted at hospital with sore cough, dyspnoea and dysgeusia. Initially, she presented with typical pulmonary infiltrates. However, on day 6 after admission, the patient's clinical status deteriorated rapidly and diagnosed with severe SARS-CoV-2 infection PCR positive. So, dexamethasone and five days remdesivir treatment was initiated. Initially, treatment was overall well tolerated. The fourth course of remdesivir was given by peripheral intravenous injection into the radial vein at the left wrist using an infusion pump. Remdesivir 100 mg in 250 mL (concentration of 0.4 mg/mL) was infused within 120 min (2.08 ml/min). Fifteen minutes before completing remdesivir infusion, the patient complained of moderate pain around the site of injection. It was suspected an extravasation. On clinical examination, the patient had an approximately 4 x 6 cm swollen area without erythema (see Figure 1A). General unspecific measures to treat extravasations were taken immediately as per our protocol: infusion was stopped and nurse aspired 5ml approximately, removed the needle, elevated the limb and called reference physician. According to acidic nature of remdesivir, it was recommended warm applications (dry warm compresses) for 15 minutes, every 8 hours, for 48 hours. Several medical controls were scheduled, and after 2 days after implementing these measures, patient recovered without complications (figure 1B). After ten days of follow-up, no sequel was observed, and patient was happily discharged home.

As far as we concerned, this is the first reported case of remdesivir extravasation with successful management in the literature treated with only dry warm. As described recently, hyaluronidase could be also an option after infiltration of acidic drugs to disperse and dilute the infiltrated drug (specially high amount of drugs) [1, 4]. However, local injections of hyaluronidase can cause side effects such as local pruritus and allergic reactions [5].

Remdesivir has been authorized for emergency use in patients with severe SARS-CoV-2 infection as it reduced the median time to recovery from COVID-19 in a randomized controlled trial [6]. After a systematic review of published literature about remdesivir extravasations, no matched was obtained. General guidelines of non-cytotoxic extravasations recommend general measures as described before. Remdesivir was slightly acid (pH=4.11). Acid exposure commonly leads to cellular desiccation, coagulative necrosis, and eschar formation. Edema, vasoconstriction, sloughing, and ulceration are common manifestations of acid-induced tissue injury. Management of acidic infiltrations remains supportive. Elevation, warm compresses, and attempts to remove the extravasated material are common nonpharmacologic treatment approaches [7].

The use of local warming therapy (dry heat) is based on the theory that it enhances vasodilation, thus enhancing the dispersion of the vesicant agent and decreasing drug accumulation in the local tissue. The use of local warming is recommended for the extravasation of non–DNA-binding vesicants.

The correct knowledge of remdesivir management, includ-

Correspondence:
David Conde Estévez
Department of Pharmacy, Hospital Universitari del Mar. Passeig Marítim 25–29, E-08003 Barcelona, Spain.
Phone: +34–93–2483851 - Fax: +34–93–2483256.
E-mail: dconde@hospitaldelmar.cat

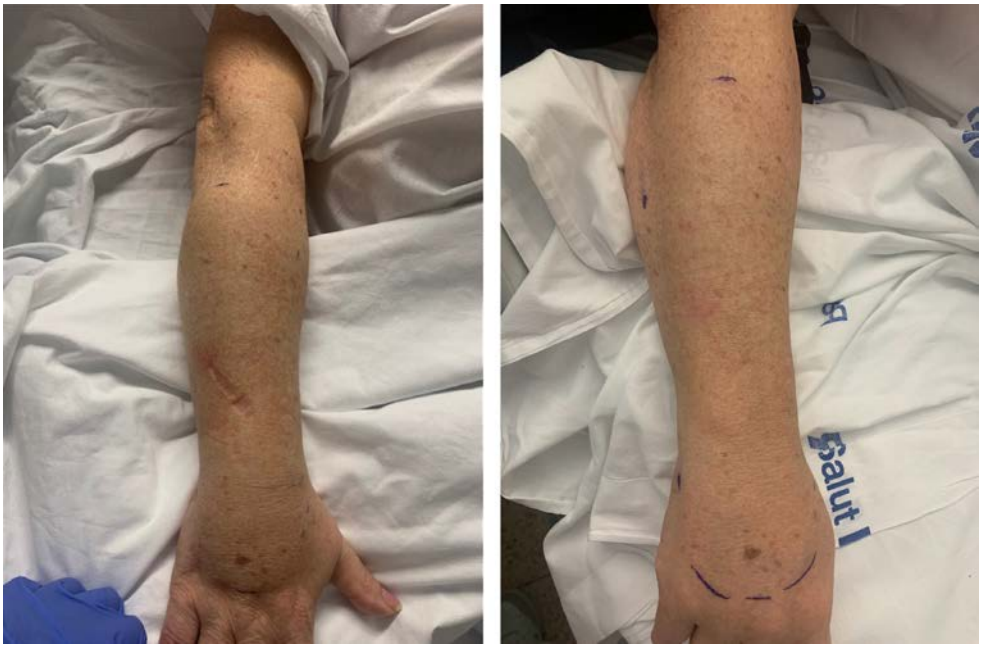


Figure 1 | **Macroscopic aspect of the lesion the day 0 (A) and day +2 (B).**

ing that of possible extravasations is essential since, despite its controversial use, the drugs available for COVID-19 disease are very limited. **According to our case report, remdesivir extravasation may be managed effectively with only dry heat and general conservative measures.**

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1 David V, Christou N, Etienne P, Almeida M, Roux A, Taibi A, Mathonnet M. Extravasation of Noncytotoxic Drugs. Ann. Pharmacother. 2020;54(8):804–14. doi;10.1177/1060028020903406.

2 Fidalgo JAP, Fabregat LG, Cervantes A, Margulies A, Vidall C, Roila et al. Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines † on Behalf of the ESMO Guidelines Working Group *. ESMO Updat. Clin. Pract. Guidel. 2012;23:vii167–vii173. doi;10.1093/annonc/mds294.

3 Kumar N, Kumar A, Pradhan S, Kumar A, Singh K. Painful Blisters of Left Hand Following Extravasation of Remdesivir Infusion in COVID-19. Indian J. Crit. Care Med. 2021;25(2):240-241. doi;10.5005/JP-JOURNALS-10071-23732.

4 van Merendonk LN, Leeuwerik AF, den Brok MWJ, Hekking PW, Korevaar DA, Jacobs CJ et al. Peripheral Infiltration of Remdesivir in 3 Patients with COVID-19: Case Series and Discussion. Am J Health Syst Pharm. 2021. doi;10.1093/AJHP/ZXAB197.

5 Jung H. Hyaluronidase: An Overview of Its Properties Applications and Side Effects. Arch Plast Surg. 2020;47(4):297-300. doi;10.5999/APS.2020.00752.

6 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813–1826. doi;10.1056/nejmoa2007764.

7 Reynolds PM, Maclaren R, Mueller SW, Fish DN, Kiser TH. Management of Extravasation Injuries: A Focused Evaluation of Noncytotoxic Medications. Pharmacotherapy 2014;34(6):617–632. doi;10.1002/phar.1396.