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Review

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Insights for COVID-19 in 2023

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ABSTRACT

Predictions for a near end of the pandemic by the World Health Organization should be interpreted with caution. Current evidence indicates that the efficacy of a fourth dose of classical mRNA vaccines (BT162b2 or mRNA-1273) is low and short-lived in preventing SARS-CoV-2 infection in its predominant variant (Omicron). However, its efficacy is high against severe symptomatic infection, hospitalization and death. The new vaccines being introduced are bivalent and active against the Omicron variants. Potential new vaccines to be introduced in the coming year include a vaccine based on a recombinant protein that emulates the receptor binding domain of the Spike protein under development by the Spanish company Hipra, as well as vaccines for nasal or oral administration. Available information suggests that vaccines against COVID-19 can be administered in association with influenza vaccination without particular complications. New drugs against COVID-19, both antiviral and anti-inflammatory, are under investigation, but this does not seem to be the case with monoclonal antibodies. The indication to use masks in some circumstances will be maintained next year in view of the accumulation of scientific data on their efficacy. Finally, the long COVID or Post-COVID syndrome may continue to affect a very high proportion of patients who have had the disease, requiring combined diagnostic and therapeutic resources.

Keywords: COVID-19, SARS-CoV2, Vaccination, bivalent vaccines, nasal and oral vaccines, investigational drugs against SARS-CoV2, use of masks, Long-term COVID

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Perspectivas de COVID-19 para 2023

RESUMEN

Las predicciones para un próximo fin de la pandemia de la Organización Mundial de la Salud deben interpretarse con precaución. La evidencia actual indica que la eficacia de una cuarta dosis de las vacunas clásicas ARNm (BNT162b2 o mRNA-1273) es baja y de corta duración para prevenir la infección de SARS-CoV-2 en su variante predominante (Omicron). No obstante, su eficacia es alta frente a la infección sintomática grave, hospitalización y muerte. Las nuevas vacunas que están siendo introducidas son bivalentes y activas frente a las variantes Omicron. Entre las potenciales nuevas vacunas que se introducirán en el próximo año, se encuentra una vacuna basada en una proteína recombinante que emula el dominio de unión al receptor de la proteína Spike en desarrollo por la compañía española Hipra, así como vacunas de administración nasal u oral. La información disponible apunta a que las vacunas frente al COVID-19 podrán administrarse asociadas a la vacunación antigripal sin particulares complicaciones. Se encuentran en investigación nuevos fármacos frente a COVID-19 tanto antivirales como anti-inflamatorios pero no parece ocurrir lo mismo con los anticuerpos monoclonales. La indicación de utilizar mascarillas en algunas circunstancias se mantendrá el próximo año en vista a la acumulación de datos científicos sobre su eficacia. Finalmente, el síndrome del COVID largo o Post-COVID puede que siga afectando a una proporción muy elevada de los pacientes que sufrieron la enfermedad, requiriendo recursos diagnósticos y terapéuticos combinados.

Palabras clave: COVID-19, SARS-CoV2, Vacunación, vacunas bivalentes, vacunas nasales y orales, fármacos en investigación frente a SARS-CoV2, uso de mascarillas, COVID-largo

INTRODUCTION

At present, many uncertainties persist about the situation and, particularly, about the future of the COVID-19 pandemic. Looking ahead to the year 2023, the most important uncertainties are related to the future of this infection and this disease. We do not know very well what can be expected from the booster vaccination of the population already vaccinated with a fourth dose of the classical vaccines, nor do we know much about the advantages and potential risks of re-vaccination with bivalent vaccines that include the most recent variants in their spectrum.

There are other uncertainties related to the treatment of the disease, the use of masks and post-COVID syndrome. Firstly, most experts do not know what to expect in terms of new drugs against COVID-19 in the coming year. Secondly, part of the population is already wandering around without masks while another persists in their use and the recommendations of the health authorities are, to say the least, ambiguous in the balance between scientific evidence and political expediency. Finally, time has not yet fully clarified what can be expected from the so-called post-COVID syndrome or long COVID, its clinical reality, its therapeutic needs and the healthcare resources it will require during the coming year.

With these doubts "in mind", the Scientific Committee of COVID-19 and Emerging Pathogens of the Illustrious College of Physicians of Madrid (ICOMEM) has formulated a series of specific questions on the aforementioned topics. The present work gathers the result of these deliberations, in which the best information found in the literature at the time of consultation has been included, to which our opinion has been added when the level of evidence was not ideal.

IS THE WHO'S PREDICTION OF A NEAR END OF THE PANDEMIC REALISTIC?

In a statement in mid-September 2022, the Director General of the World Health Organization (WHO) compared the race to control the COVID-19 pandemic to a marathon and said, "Last week's death toll from the pandemic was the lowest since March 2020. We are in a position to win, but now is the worst time to stop running, it's time to accelerate. We already see the finish line." Like all policy makers, Tedros Ghebreyesus combined evidence, such as the number of deaths, with calls for action in the various countries; and to reinforce the message in the war against the coronavirus, he came to say, like a good strategist, that victory is possible and close at hand [1]. Probably everything he said is true, although WHO senior epidemiologist Maria van Kerkhove also emphasized that "we expect future waves of infections, potentially at different times around the world caused by Omicron subvariants or even different variants of concern."

It is true that never before in the pandemic have we been so prepared to control it, since the population has a high degree of protection against serious infection, derived both from vaccination and from the high frequency of acquired infections (often repeated). In addition, vaccination boosters (against the original Wuhan variant and Omicron) are already being massively administered to the most vulnerable (over 60 years of age or with severe chronic pathologies), which will strengthen protection. On the other hand, the virus will probably continue to circulate, because immunity or vaccines do not substantially reduce the risk of infection; although this will lead to a certain increase in the number of severe cases during periods of high transmission, with the consequent overload of the health system, it should not produce a proportional increase in hospitalizations or a dramatic increase in deaths and will contribute to maintaining a high level of community protection. A different issue is the lack of knowledge about the dynamics of interaction between coronavirus and other respiratory viruses (e.g. influenza), making it difficult to anticipate the total number of respiratory infections, as well as their health impact. These perspectives, quite positive, could change due to an important mutation(s) in the virus that would increase its virulence and/or immune escape. There is nothing concrete to suggest that this will happen, but it is not possible to rule it out with this virus either. However, the virus is not intelligent and does not do what it wants; only what we let it do. Therefore, the sensible thing to do is to continue working to control its damage, by monitoring the emergence of new variants of potential relevance, vaccine boosters and, if necessary, the temporary reactivation of some control measures (e.g. use of masks, ...). We share the optimistic message of the WHO, we trust in a favorable evolution of the pandemic, but we will continue to be alert and to work "to reach the goal", as it may be close.

WHAT IS THE EVIDENCE OF PROTECTION OF NEW DOSES OF ANTI-COVID-19 VACCINES WITH CLASSIC VACCINES?

Current evidence indicates that the efficacy of a fourth dose of classical mRNA vaccines (BT162b2 or mRNA-1273) is low and short-lived in preventing SARS-CoV-2 infection in its predominant variant (Omicron). Despite this, it is highly effective (about 80%) and long-lasting against severe symptomatic infection, hospitalization and death.

The vaccines achieved to curb the SARS-CoV-2 pandemic have been the most decisive achievement in modifying very favorably the severity of the pandemic, mainly for the large risk group of elderly patients [2,3]. Thus, the advent of the vaccines provided, against pre-Omicron variants, about 87% protection against hospitalization and death from severe COVID-19 disease after a two-dose schedule of BNT162b2 (Pfizer), mRNA-1273 (Moderna, or ChAdOx1-S (Oxford/Astrazeneca) [3]. Subsequently, the drop in immunity showed the need for a booster dose (third dose), after six months of complete vaccination, with any of the commonly used mRNA-based vaccines, thus significantly reducing the chances of infection or reinfection with SARS-CoV2. However, the emergence of SARS-CoV-2 variant B.1.1.529 (Omicron) changed the pandemic landscape once again. The protective capacity of vac-

cination against infection has been decreasing even lineage by lineage [4]. Omicron has infected people who have complied with primary vaccination doses, who have boosted their immunity with booster doses of appropriate immunogens, and even who have had the disease before or after these compliances [4-6]. However, their efficacy in reducing mortality and severe disease rates has been maintained with little loss, both for the original strains for which they were designed and for successive strains (with notable antigenic variation in neutralization targets). The sixth and seventh waves have shown similar incidences of infection in those over 60 years of age as in the first waves, especially in the elderly and frail population, both in the community and in social and healthcare centers [7], so the clamor for booster vaccines has once again reached its peak [8]. Observational studies from Israel, during a predominant Omicron period, revealed that a fourth dose of BNT162b2 in persons over 60 years of age produced low protection in preventing infection of short and uncertain duration (between 3 to 8 weeks) but with lower rates of severe disease, (75% effective against COVID-19 mortality compared to the third dose) [9-11]. In all these studies, subjects under 80 years of age were included for the most part and residents of long-stay centers, who represented a very small percentage of the sample, were excluded. Subsequently, therefore, two large retrospective population-based cohort studies conducted in social and health centers for the elderly showed similar results with both mRNA-1273 and BNT162b2 (up to 80% reduction in hospitalization and mortality due to COVID-19 from a fourth dose) [11,12]. These results have led some countries, including Spain, to include this fourth dose in this population group.

Fortunately, successive doses have not led to an increase in adverse reactions. There was no increase in the local reaction to the inoculation or in the systemic symptoms associated with the immediate days following the dose [13]. Myocarditis as a side effect of RNA-mRNA vaccines, more associated with adolescents and young people, is not a drawback. In fact, there seems to be a lower incidence than in the primary vaccination series [14]. It is confirmed that the initial fear of generating antibodies that would block an effective neutralizing response (potentiation of the disease with the vaccine), does not occur with booster doses, as it has not occurred in the initial vaccination.

Therefore, the possible indication for classical vaccines should be reduced to groups at higher risk of mortality when bivalent vaccines are not available. In our opinion, a fourth dose with classical vaccines in the general population would provide a minor benefit until vaccines including the new Omicron variants become available.

WHAT VARIANTS WILL THE NEW VACCINES INCLUDE, AND WHEN WILL THEY BE AVAILABLE?

The vaccination strategy against SARS-CoV-2 infection until the summer of 2022 in Spain has been based on the use of prepared vaccines based on the original Wuhan strain. Essentially, the Pfizer and Moderna vaccines have been used, both based on messenger RNA technology for the expression of the SARS-CoV-2 spicule (S) protein, and, to a lesser extent, the AstraZeneca vaccine (AZD1222), based on a nonreplicating recombinant viral vector (adenovirus) expressing the S protein. In all cases, the immunogenic antigen of these vaccines was identical to that of the original Wuhan strain of SARS-CoV-2 [15]. As mentioned above, the strategy followed to date has been shown to be effective against severe disease, hospitalization and mortality, but not against reinfection.

The rapid emergence of successive variants of concern, with a large number of mutations (Omicron variants have more than 50 mutations in their spicule), has led to the development of a different strategy with vaccines based on these new variants [16-18]. This is mainly due to the loss of efficacy of classical vaccines against infection by successive new variants and the need for continuous booster doses to maintain acceptable levels of neutralizing antibodies to protect against infection and successive reinfections [19]. It is evident that re-vaccination with vaccines prepared against the original strain does not seem to be a wise strategy, especially in a country with high vaccination and reinfection rates. In addition, data have been published indicating that the possible use of vaccines with different antigens does not diminish efficacy and favors the immune response, a situation endorsed by both the EMA and the FDA in the approval of new vaccines [20-22].

The accumulated experience with the use of mRNA vaccines and the relative ease of their manufacture, including that of the new variants, the few doubts about their safety and the robust pharmacovigilance system, as reported by the vaccine expert committees, suggest a dual strategy: vaccination and revaccination with a new vaccine whose composition would be immunogenic against the original SARS-CoV-2 strain and also against the most recent variants. This would provide adequate coverage against the emergence of possible new variants close to the original Wuhan variant, as occurred with Omicron, which is closer to it than to its predecessor in time, the Delta variant, and the eventual emergence of variants or subvariants of Omicron that dominate the current (October 2022) panorama of infections and reinfections [17,18,23].

Therefore, the EMA and the FDA have approved the so-called bivalent vaccines adapted to the new variants [20-22]. They are mRNA vaccines against the original Wuhan strain and the Omicron BA.1 variant (Pfizer and Moderna) and also against the original strain and the Omicron BA.4/BA.5 variant. All of them are included in the recommendations for vaccination against COVID-19 in Spain in the early fall of 2022 [24].

For the moment, regulatory agencies require safety studies of vaccines against new variants of SARS-CoV-2 and, although they have an accelerated evaluation process, it is possible that, in the future and given the need to create new vaccines against emerging variants, this procedure will be relaxed and follow a model similar to that of influenza vaccines. The latter are clearly safe, with fewer safety studies required for their commercialization. However, this situation does not exempt the performance of follow-up studies in accordance with pharmacovigilance standards.

WHAT WILL BE THE FUTURE ROLE OF HIPRA'S SPANISH VACCINE?

The European Medicines Agency (EMA) is evaluating the Spanish Hipra vaccine against COVID-19, as a booster dose for those who have received the primary vaccination regimen with a different vaccine.

The Hipra vaccine is based on a recombinant protein that emulates the receptor binding domain (RBD) of the Spike (S) protein of the Alpha and Beta variants of the SARS-CoV-2 virus. This antigen is accompanied by an adjuvant that enhances the immune response.

Clinical trials in adults compare the immune response to Hipra's vaccine, through the level of antibodies against SARS-CoV-2, with that observed with Pfizer's messenger RNA vaccine. A total of ten Spanish hospitals are currently participating in a clinical trial to evaluate the efficacy of Hipra's COVID-19 vaccine, as a fourth dose, in subjects previously vaccinated with three doses of the Comirnaty vaccine (Pfizer), provided that the last dose was administered within the previous 6-12 months and that they had not had COVID-19. A 30-month follow-up has been established for immune response and safety. The most common adverse effects have been pain in the area of inoculation, headache or fatigue, which have disappeared in the following days and have not prevented them at any time from leading a normal life [25].

Preliminary data show a good immune response against beta and Omicron variants of SARS-CoV-2. A recent study shows a strong immune response against all variants studied (Wuhan, Beta, Delta and Omicron (BA.1) at 14 and 98 days, being these increases statistically superior to those obtained with the booster dose with the Pfizer-BioNTech vaccine at 98 days against Beta, Delta and Omicron (BA.1) variants, and at 14 days against Beta and Omicron (BA.1) variants) [26,27]. The biotech pharmaceutical company Hipra has shown in recent analyses that its vaccine also confers protection against the Omicron BA.2 and BA.4/BA.5 subvariants, as evidenced by an increase in neutralizing antibodies against the BA.2 and BA.4/BA.5 subvariants of Omicron. These data would indicate a more sustained response over time, suggesting a more durable and effective protection against the new circulating variants.

The Spanish Hipra vaccine has demonstrated a good safety profile. Among the advantages of this vaccine is that it can be stored at 2 to 8 ºC, which would facilitate its logistics and distribution. It is currently ready for intramuscular (IM) use and clinical trials are underway.

WHAT ROLE CAN NASAL VACCINES AGAINST COVID-19 PLAY?

COVID-19 vaccines administered IM have been shown to effectively reduce disease severity and, to a lesser extent, infection or transmission [28,29], as they allow the replication of SARS-CoV-2 in the upper respiratory tract of vaccinated persons and the elimination and transmission of the virus [30,31]. Moreover, they do not induce a neutralizing IgA antibody titer effectively in the mucosa of the upper respiratory tract, which is necessary to achieve sterilizing immunity against SARS-CoV-2.

In contrast, mucosal vaccines, administered orally (OV) or intranasally (IN), can provide a more rapid and intense local antiviral immune response in the mucosa of the upper and lower respiratory tract, mediated primarily by neutralizing IgA secretion [30,32]. Activation of mucosal protective immunity offers the possibility of inhibiting viral multiplication and decreasing virus excretion through the respiratory tract mucosa. In this way it acts as a first-line barrier to virus entry, as well as against spread to the lungs. It can also prevent the transmission and spread of SARS-CoV-2, contributing to achieve herd immunity in the population [30]. In addition, these mucosal vaccines induce a potent systemic immune response against COVID-19 [33].

Inhaled (IN) mucosal vaccines appear to have great potential for preventing highly contagious respiratory viral infections such as measles, influenza and COVID-19 [34]. There are precedents with vaccines administered by OV or IN that have demonstrated their effectiveness in the clinical management of gastrointestinal and respiratory tract infections (poliovirus, rotavirus, adenovirus, influenza) [30,34]. Currently, there is evidence, in experimental animal models, in favor of the ability, mainly of IN mucosal vaccines, to induce sterilizing immunity against COVID-19 [31,32,35]. However, so far the evidence in humans is limited [31].

More than 100 OV or IN vaccines against COVID-19 are currently under development worldwide, and at least 20 prototypes are already being tested in humans [35,36]. In September 2022, two adenovirus-vectored mucosal vaccines against COVID-19 have been approved for human use. In both cases they have passed Phase III clinical trials, although the results have not yet been published [36]. In China, an IN vaccine has been approved as a booster after IM primary immunization, both with the same composition. This booster has been shown to be safer and persistently more immunogenic than the IM booster, although the immune response decreases over time [37]. In India, a vaccine administered by nasal drops has been approved for primary immunization in humans [28,32]. Among these new IN vaccines is a Spanish vaccine developed by the company Hipra, which contains recombinant proteins of the alpha and beta variants of SARS-CoV-2, currently under investigation in a phase III clinical trial.

Respiratory mucosal vaccines against COVID-19 offer several logistical advantages over current IM, which would facilitate mass vaccination campaigns: greater stability and shelf life of the vaccines, allow self-administration, better compliance and lower technological requirements for storage, distribution, and transport [34,36].

CAN THE NEW VACCINES BE ADMINISTERED TOGETHER WITH THE INFLUENZA VACCINATION?

The interaction between influenza and COVID-19 has been of interest since the beginning of the pandemic. Co-infection

by both viruses, although rare, has been [38], associated with more severe respiratory symptoms and longer ventilatory support times [27]. In addition, the possibility was initially raised that the influenza vaccine might have a protective effect against SARS-CoV2 infection, reducing both the risk of infection and limiting the severity of the disease [39,40]. In animal models, it has been observed that joint vaccination against influenza virus and SARS-CoV2 generates effective protection and even potentiation of both vaccines [41]. In addition to this rational basis for joint vaccination, there is the logistical problem of having to carry out two vaccination campaigns almost simultaneously. The possibility of administering both vaccines in a single event would reduce organizational costs and facilitate adherence of the population [42]. In order to analyze the safety of this strategy, several co-administration studies have been launched [42-44]. Overall, these investigations have demonstrated efficacy and safety, although the evidence may be considered limited. The three trials included small groups (679 cases in the largest of them) and the vaccination strategies differed both in the selection of the type of influenza vaccine and of the vaccine against SARS-CoV2 (different in each of them and therefore difficult to generalize). However, the fact that no serious safety incidents have been found, despite using the most immunogenic vaccines of all those tested, mRNA-123 for SARS-CoV2 and a high-dose quadrivalent vaccine for influenza, supports this strategy [44].

Therefore, it seems reasonable to proceed with simultaneous vaccination against influenza and COVID-19 in the general population at risk. Nevertheless, it may be prudent to separate the vaccines in those persons who have had relevant adverse effects from either of them. Nor would it be recommended to combine them in young people, especially males under 40 years of age, in whom adverse effects may be more frequent [45] and the risk of both diseases is low. In future campaigns it is likely that vaccines will be available to protect against both viruses in a single dose [46-48] and even against SARS-CoV2 and pneumococcus [49], but its efficacy and safety have yet to be demonstrated in humans.

WHAT INDICATIONS MAY THE USE OF MASKS HAVE THROUGHOUT 2023?

The use of facemasks is intended on the one hand to reduce the emission of particles by infected persons, both symptomatic and asymptomatic ("source control"); and on the other hand to protect the uninfected population by reducing inhalation of particles ("user protection"). Therefore, the use of facemasks in pandemic control seems to be fully justified and, in fact, their widespread use has been a basic element in the management of the COVID 19 pandemic. After some initial erratic or contradictory indications, most governments, although not all, introduced mandatory standards for their use in both open and closed spaces. The reason for these differences between countries, apart from the socio-political characteristics of each of them, has been justified by alleging a lack of scientific evidence for their use. And the fact is that, although their mechanical capacity to filter medium and small particles has been demonstrated, they do not have the capacity to filter small-sized particles [50-53], its clinical efficacy, according to the principles of scientific evidence, was not sufficiently demonstrated up to the time of the pandemic. Thus, a Cochrane review of 2020, based on observational studies and few clinical trials, which did not include results of impact in COVID-19, concluded that the evidence on the protective capacity of masks in the clinic was weak. These results were also the conclusion of a first review, published early in 2020, already conducted with studies in SARS-CoV-2 infection [54, 55].

However, since these first months, more and more data have emerged that demonstrate the efficacy of the masks [56]. Studies comparing results in the general population with those of healthcare personnel show that these results are better in the latter [55,57,58], probably due to the higher exposure burden. It was also observed that the more widespread the population use of the mask, the greater the impact on transmission [58]. It should be noted that a recent study in our country shows that up to 89% of the surveyed population correctly followed the rules of use [59]. This is in line with other publications that show that the existence of clear and strict regulations, such as those in our environment after the hesitant beginnings, favor adherence and the perception of risk (high in the Spanish population) [60].

Although there is no doubt about the contribution that the use of masks has had in the control of the pandemic, the mandatory use of masks has been progressively limited. The regulation was extended to all public spaces, then to enclosed spaces, and finally to health institutions and public transport, given that a large part of the population is vaccinated, the incidence of COVID-19 is relatively low, and health care systems are not under stress [61].

The reality is that the use of masks is currently only contemplated in healthcare institutions in most countries. In Spain, the use of masks is still mandatory in health care centers and public transport, although in the latter area it is becoming increasingly controversial (some communities are already advocating its elimination).

Until now, CDC recommendations did not advocate the elimination of facemasks in enclosed spaces, adjusting them to criteria of disease incidence and population vulnerability. However, as of September 28, they assumed their suppression even in hospital centers, if there is low transmission and the population is not vulnerable. As for public transport, it is not even mentioned despite the fact that very recently an article in JAMA echoes the results obtained in a study sponsored by the California Department of Public Health, which shows the higher risk of COVID infection in public transport workers compared to other workers [62]. In our environment, several factors must be taken into account. In them, the pandemic can by no means be considered over, and although hospital and intensive care admissions are low and do not generate any concern, the incidence is medium, not low.

We are facing the winter season, in which in addition to SARS-CoV-2 infection, influenza and other respiratory diseases, such as Respiratory Syncytial Virus (RSV), must be taken into account. In this sense, it seems reasonable to establish the following recommendations for the use of masks: 1) health and social-health centers, both health personnel and visitors; 2) public transport; 3) vulnerable persons and their caregivers in any enclosed space, especially if a social distance cannot be maintained, while the pandemic state persists; 4) subjects with symptoms of acute respiratory infection.

This Committee would like to emphasize that, given the possible feeling of inconsistency due to the appearance of variable recommendations, the public should be given a clear message that variability of recommendations may be inevitable and is determined by the changing circumstances of the pandemic.

SHOULD CHILDREN BE INCLUDED IN UPCOMING ANTI-COVID VACCINATION PROGRAMS?

Childhood vaccination started 6 months after adult vaccination, with different age groups being progressively incorporated depending on the availability and authorization of vaccines. In May 2021, adolescents aged 12 to 19 years were vaccinated first, with mRNA vaccines equal to those for adults. Then, in November 2021, children aged 5 to 11 years were vaccinated with two new vaccines of lower antigenic load. Finally, in June 2022, the FDA approved the following vaccines [63] and the CDC recommended [64] vaccinate children from 6 months of age with mRNA vaccines of lower antigenic load (30mcg for both manufacturers).

Vaccination of adolescents in the United States with 2 doses of Comirnaty [65], demonstrated high effectiveness against COVID-19 in real life (94% protection against hospitalization and 98% against ICU admission, where 7 deaths occurred in unvaccinated patients); despite the fact that at that time (July-October 2021) the Delta variant was the predominant circulating strain. In children aged 5-11 years, vaccine effectiveness against infection was lower than expected, as shown by studies in Italy [66] and New York [67]. In Italy [66], vaccine effectiveness in preventing severe forms of COVID-19 could be demonstrated, despite the rapid decline of vaccine antibodies in the following 40-80 days post-vaccination. Several studies have shown that healthy children are at low risk of severe COVID-19 complications, regardless of their vaccination status [66-68]. These vaccination results in children aged 5-11 years are probably influenced by their late incorporation to vaccination, when many had already been infected, exposure to new variants of the virus not contained in the original vaccines and the use of vaccines with low antigenic load, so that protection is lower than that achieved in other age groups [69].

mRNA vaccines in children have been shown to be safe post-implantation [11]. In the United States, after 38 million doses administered in children aged 5-17 years, post-vaccination myocarditis (the most serious complication) was a rare event, of variable incidence according to age (4.3 cases per million doses in children aged 5-11 years), and of spontaneous evolution to cure [70]. The remaining adverse effects, although more frequent (fever, headache, asthenia, myalgia, etc) were mild and rapidly resolved without sequelae.

We can summarize that, in our environment, children and adolescents currently have good protection against COVID-19 due to vaccination and to the fact that they have been continuously exposed, infected and reinfected by the virus and its variants during the last two years of the pandemic.

For the reasons indicated above, at the present time and probably in the medium term, it does not seem a priority or urgent to include the pediatric population in the new anti-COVID-19 vaccination programs. Bivalent vaccines are only authorized for adults and those over 12 years of age, and we have no information on trials underway for pediatrics. The future of childhood vaccination will depend on the evolution of the pandemic, which could modify the current situation, and on the availability and authorization of the new vaccines (bivalent) in children. The Spanish Ministry of Health [71] recommends : 1) maintain childhood vaccination with the original mRNA vaccines against SARS-CoV-2 currently available and licensed; 2) complete vaccination (2 doses in healthy children and 3 doses in immunocompromised), respecting the intervals between doses according to age and vaccine (older than 12 years with intervals between doses of the primary series will be 3 weeks for Comirnaty and 4 for Spikevax; in children aged 5-11 years the interval is 8 weeks; in immunosuppressed or immunosuppressive children the primary series is 3 doses of vaccine, the last dose separated from the previous one by at least 28 days); 3) do not revaccinate children until the entire adult population has been vaccinated. It is highly recommended to vaccinate children against influenza to prevent the co-infection of COVID with influenza, which can worsen the pandemic and its complications, especially in adults. This has been considered by the Community of Andalusia, which in a pioneering way has authorized in October 2022, the universal vaccination against influenza in all children between 6 and 59 months of age.

IS THE INTRODUCTION OF NEW DRUGS EFFECTIVE AGAINST SARS-COV-2 EXPECTED IN 2023?

The treatment of SARS-CoV-2 has been enriched by the incorporation of drugs with different mechanisms of action (antivirals, monoclonal antibodies, anti-inflammatory drugs, etc.), which have been shown to be effective in different clinical situations (mild disease, moderate/severe disease). In some cases, they have been the result of original research and, in others, a consequence of the repositioning of drugs designed for other indications. In some way, the needs of most patients with COVID-19 have been covered.

Despite the availability of existing drugs, research continues to increase the treatment options for the disease. In this regard, the efficacy of some existing drugs is being explored in indica-

tions other than those approved or in specific situations. Various clinical trials are under way: nirmatrelvir/ritonavir, effective in outpatients with mild disease, is being tested in hospitalized patients with severe disease; remdesivir is being studied in oral formulation; various antivirals are being investigated in the special group of immunocompromised patients, who are particularly in need of therapeutic options for severe disease.

As for new drugs, mainly antivirals and, to a lesser extent, anti-inflammatory drugs are being developed. No new monoclonal antibodies are at an advanced stage of research. Without claiming to be exhaustive, we discuss below some of the drugs in advanced development that could be marketed during 2023.

With regard to new antivirals, we will discuss ensitrelvir, ensovibep and aplidin. Ensitrelvir (S-217622, Xocova®) is an oral 3CL protease inhibitor developed by the company Shionogi [72]. Has activity against all known variants of SARS-CoV-2, including the recently released Omicron BA.2.75 subvariant [73]. In phase 2 clinical trials conducted in Japan and Korea, the drug showed a significant and rapid decrease in viral load compared to placebo, with no significant toxicity, but no effect on symptom progression [74]. Phase 3 trials are currently being completed [75].

Ensovibep belongs to a novel class of designer proteins (ankyrin) that can block all three units of the SARS-CoV-2 protein S trimer and inhibit ACE2 binding with high potency [76]. It is administered as a single dose intravenously. Following promising results in a Phase 2 trial, demonstrating a 78% reduction in the risk of hospitalization, a Phase 3 clinical trial has been conducted in patients with severe disease. In this trial, compared to placebo, ensovibep did not improve the clinical outcome of patients hospitalized with COVID-19 who were receiving standard of care, including remdesivir, although it was shown to be safe. The trial was stopped due to futility and the intended sample size was not reached [77].

Aplidin (plitidepsin) is a marine cyclic peptide that inhibits SARS-CoV-2 replication, at nanomolar concentrations, by inhibiting host protein translation elongation factor 1A [78]. A Phase 1 clinical trial has been conducted in 46 hospitalized patients with COVID-19, which demonstrated a favorable safety profile and decreased viral load by up to 3.8 log10 per day 31 [79]. Phase 2-3 trials are currently underway and are planned in special subgroups of immunocompromised patients.

Regarding anti-inflammatory drugs, sabizabulin is a new investigational oral microtubule disruptor with antiviral and anti-inflammatory activities. It was originally developed to treat metastatic castration-resistant prostate cancer [80]. Because of its mechanism of action, it has been investigated to treat pulmonary inflammation in patients with COVID-19. In a double-blind phase 3 clinical trial, sabizabulin reduced the risk of death by 55%, independent of standard of care treatment received, baseline WHO scores, age, comorbidities, vaccination status, SARS-CoV-2 variant and geography [81]. Although the company has applied for emergency clearance by the FDA, the small sample size (204 patients) may determine that its efficacy is lower than published.

WHAT WILL BE THE STATUS OF THE SO-CALLED EXTENDED OR LONG-TERM COVID IN 2023?

Since the beginning of the SARS-CoV-2 pandemic, it has been documented that a significant percentage of patients had persistent alterations of the disease after the acute episode, known as post-COVID syndrome, persistent COVID or Long-Term COVID. Its incidence, which varies according to the criteria used, ranges between 20-90%.

In 2021, WHO published a consensus definition "post-COVID-19 condition occurs in persons with a history of probable or confirmed SARS- CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others that generally have an impact on daily functioning. Symptoms may recur, after initial recovery from an acute episode of COVID-19, or persist from the initial illness. Symptoms may also fluctuate or relapse over time." [82].

This Committee has already taken a position in a document on how the health care of these patients should be organized, with a multidisciplinary vision, through protocols and clinical pathways, and on the uncertainty derived from the real impact of this syndrome in the coming years [83].

There are still many unknowns in the current understanding of the pathogenesis of prolonged COVID. There are current factors that could influence the impact of this syndrome, such as vaccination, the emergence of new variants of the virus, as well as other social factors that could influence the incidence and severity of these sequelae [84].

Studies with low level of evidence (grade III, case-control, cohort studies) indicate that vaccination prior to SARS CoV2 infection may reduce the risk of prolonged COVID, as well as a reduction of persistent symptoms after vaccination with the first dose and a sustained improvement of symptoms after the second dose, even in patients with significant functional impairment [85,86].

Most studies of prolonged COVID include early variants of the virus. Recent results indicate that early variants of Omicron are associated with an approximately 50% reduction in the risk of developing prolonged COVID compared with delta variant [87,88].

Despite the paucity of data, the number of patients with persistent COVID is expected to be very high given the magnitude of the pandemic. Considering a low estimate, more than 9.6 million people in the U.S. may have developed prolonged COVID. This poses a challenge to healthcare systems. In addition, very high related costs are estimated ($2.6 billion US) given the impact on work activity [89]. Other studies, such as the one carried out in the Netherlands, show that one in eight patients are affected by persistent symptoms [90].

Although several clinical trials are currently underway, there is no specific treatment for persistent COVID. While

awaiting results that can guide us towards more effective and specific therapies, symptomatic treatment is mostly used, both pharmacological (analgesics, anti-inflammatory drugs, bronchodilators, antitussives, antiemetics, antidepressants, anxiolytics, etc.) and food supplements and vitamin complexes (vitamin B12, vitamin D, omega 3). Psychological and emotional support is also essential for these patients and the need for multidisciplinary intervention of rehabilitation and stimulation programs (occupational therapy, physiotherapy) should be considered [91].

In the initial phase of the pandemic, monographic units and multidisciplinary teams were created for the follow-up and care of these patients. In the current phase, many of these devices have considered restructuring these monographic units, given the reduced number of COVID patients, assigning symptom control to the usual consultations of different specialties without having defined the optimal model to offer effective, efficient, equitable and accessible care to all patients [92].

In order to advance research and create new scientific evidence, it is necessary to have a set of results that can evaluate the impact of interventions in persistent COVID, taking into account the opinion of patients and family members. It is crucial to promote research strategies to improve knowledge of the pathophysiological aspects of the syndrome, harmonize diagnostic criteria and develop effective therapies In addition, it is necessary to have registries, ideally international, that allow progress in the knowledge of the disease and adjust the health support structures to the real needs of these patients, considering especially vulnerable or specific populations such as pediatrics [93].

The Spanish Research Network on Persistent COVID (REiCOP), led by the Spanish Society of General and Family Physicians (SEMG), has recently been set up with the collaboration of 57 scientific societies, professional associations and other entities including patient groups and associations. Its main objective is to increase the evidence regarding persistent COVID and to facilitate the care of those affected from a holistic and multidisciplinary viewpoint through clinical guidelines, training activities, the creation of a registry and the development and validation of a care scale, among others. It also includes the development of a care model adapted to the needs of patients, defining patient flows and incorporating the patient's experience.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Review

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Impact of the COVID-19 pandemic on the mental health of the general population and health care workers

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ABSCTRACT

The Health Sciences Foundation has assembled a multidisciplinary group around a series of questions about the impact of the COVID-19 pandemic on the mental health of the general population and specific groups within that population, particularly healthcare workers.

In the general population, the most prevalent mental disorders have been anxiety, sleep disorders and affective disorders, primarily depression. There has been a considerable increase in suicidal behavior, especially in young women and men over 70 years of age. There has been an increase in alcohol abuse and nicotine, cannabis and cocaine use. In contrast, the use of synthetic stimulants during periods of confinement has decreased. With regard to non-substance addictions, gambling was very limited, pornography consumption increased significantly and there was an increase in compulsive shopping and the use of video games.

Particularly vulnerable groups include adolescents and patients with autism spectrum disorders. Healthcare workers suffered an increase in depression, anxiety and post-traumatic stress, especially those who were exposed during the early stages of the pandemic. Female sex, being a nurse, proximity to patients with COVID-19, working in a rural environment and having previous psychiatric or organic illnesses were some of the most frequently repeated factors in various studies in this population group.

The media have shown a good degree of knowledge about these problems and have dealt with them frequently and from the point of view of ethics, crisis situations, such as the one experienced, have triggered not only physical but also moral claudications.

Keywords: COVID-19, SARS-CoV-2, Mental health, Depression, Anxiety, Stress, Suicide, Autism, Adolescence, Healthcare,

Impacto de la pandemia de COVID-19 en la salud mental de la población general y de los trabajadores sanitarios

RESUMEN

La Fundación de Ciencias de la Salud ha reunido a un grupo multidisciplinar alrededor de una serie de preguntas sobre el impacto de la pandemia de COVID-19 en la salud mental de la población en general y de grupos específicos de dicha población, particularmente los trabajadores sanitarios.

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En la población general, los trastornos mentales más prevalentes han sido la ansiedad, los trastornos del sueño y los trastornos afectivos, fundamentalmente la depresión. Se ha producido un aumento considerable de la conducta suicida, especialmente en mujeres jóvenes y varones mayores de 70 años. Se ha incrementado el abuso de alcohol y los consumos de nicotina, cannabis y cocaína. Por el contrario, ha disminuido el consumo de los estimulantes sintéticos durante los periodos de confinamiento. Respecto a las adicciones sin sustancia, el juego de apuestas quedó muy limitado, el consumo de pornografía experimentó un incremento notable y hubo un aumento de la compra compulsiva y del uso de videojuegos.

En cuanto a grupos particularmente vulnerables hay que destacar el de los adolescentes y el de los enfermos con trastornos del espectro autista. Los sanitarios han sido un grupo especialmente vulnerable, en particular los que estuvieron expuestos durante las primeras fases de la pandemia. El sexo femenino, el ser enfermera, la proximidad a los pacientes con COVID-19, el ejercicio en un medio rural y padecer enfermedades psiquiátricas u orgánicas previas, fueron algunos de los factores más frecuentemente repetidos en diversos estudios en este grupo de población. Depresión, ansiedad y estres postraumático fueron los trastornos más frecuentes.

Los medios de comunicación han mostrado un buen grado de conocimiento sobre estos problemas y los han tratado con frecuencia. Desde el prisma de la ética, las situaciones de crisis, como la vivida, han desencadenado claudicaciones no solo físicas sino también morales.

Palabra clave: COVID-19, SARS-CoV-2, Salud mental, Depresión, Ansiedad, Estrés, Suicidio, Autismo, Adolescencia, Sanitarios,

INTRODUCTION

The COVID-19 pandemic will soon be three years old, with catastrophic and well-known consequences on the physical health and mortality of the planet's inhabitants. Its consequences on mental health have been equally enormous and its analysis has been carried out at different times of the pandemic and with logically partial approaches. On the other hand, the conditions for altering the mental health of individuals and groups that the pandemic has entailed have been different in different places.

The Board of Trustees of the Health Sciences Foundation asked itself, at the time, a series of questions about the consequences of the COVID-19 pandemic on mental health, both in the general population, with or without previous good mental health, and in the group of health care workers. These consequences were of particular concern for the Spanish population. For this reason, a series of experts in different subjects related to the topic were brought together to try to answer these questions in the light of the scientific evidence and their own opinion and experience. After the presentation of the subject, in each of the questions and with the discussion of the whole group, a consensus conclusion was reached that tried to summarize the state of the art on the subject.

The paper that follows is the result of that process. All authors have reviewed and approved the final manuscript.

The paper is divided into a first part assessing the impact of the pandemic on the mental health of the general population and a second part on its impact on healthcare workers.

PART ONE - IMPACT OF THE PANDEMIC ON THE MENTAL HEALTH OF THE POPULATION

WHAT IS MENTAL HEALTH AND HOW IS IT DEFINED? WHERE ARE THE LIMITS OF PATHOLOGY? WHAT ARE THE METRICS THAT BEST REFLECT THE MENTAL HEALTH OF A SOCIETY?

The World Health Organization (WHO) considers good mental health to be a state of well-being in which the individual is aware of his or her own capabilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community. Just as it defines good health, not just as a lack of disease, so it does with mental health [1].

In contrast, mental disorder is a clinically significant and sustained emotional, cognitive and/or behavioral disturbance, in which basic psychological processes such as emotion, motivation, cognition, consciousness, behavior, perception, sensation, learning, language, etc. are affected. These symptoms make it difficult for the person to adapt to the cultural and social environment in which he/she lives, which can lead to some form of subjective distress (Figure 1).

Good mental health is composed of multiple dimensions that affect different areas of a person's life. In a recent review on this topic, we identified fourteen items to define good mental health (Table 1)[2,3].

Table 1 | **Items needed to define mental health**

1.- Knowledge about mental health	8. Self-care strategies
2.-Attitude towards mental disorders	9. Social skills
3.-Self-perception and values	10. Family and significant relationships
4.-Cognitive abilities	11. Physical health
5.-Academic/employment functioning	12. Sexual health
6.-Emotions	13. Meaning of life
7.-Behaviors	14. Quality of life

Conclusions:

Mental health is something that goes beyond the lack of illness and is measured dimensionally and dynamically. The boundaries of mental health and mental disorder are defined by how mental health problems influence the functioning (social, occupational, academic, family, etc.) of the individual. There are multiple variables that measure the mental health of a population, even more so if the interactions between them are taken into account.

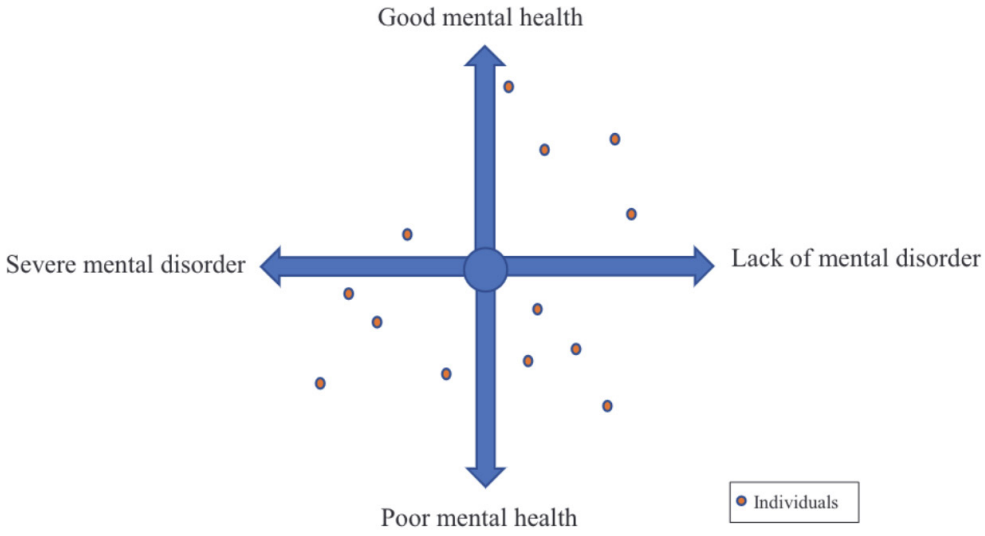

Figure 1 | **Dimensional scheme of both mental health and mental disorders, being fundamental for the latter their impact on the person's functionality.**

WHAT ARE THE MOST PREVALENT MENTAL DISORDERS?

Epidemiological studies on the prevalence of mental disorders in the community in Western European countries, including Spain, indicate, with a very consistent level of agreement, that the most common disorders are anxiety disorders, sleep disorders and affective disorders [4,5]. Many studies were conducted prior to the Great Recession of 2008 and the COVID pandemic, so from today's perspective these assessments must be considered conservative.

Specifically, estimates indicate that each year 38.2% of the European population suffers from a mental disorder, which, adjusted for age and comorbidity, corresponds to 164.8 million people affected. Common disorders are anxiety disorders (14.0%), insomnia (7.0%), major depression (6.9%), somatoform (6.3%), and alcohol and drug dependence (4%). Other less frequent disorders, but with great personal and health care repercussions, due to the seriousness they can have, are psychotic disorders, mainly schizophrenia (1.2%), bipolar disorder (0.9%) and personality disorders (1.3%). Also noteworthy is the prevalence of intellectual disability (1%), which is not a mental disorder, but is a risk factor for the presence of mental disorders and behavioral alterations (Figure 2).

In terms of entities that are concentrated in an age range, we can highlight attention deficit hyperactivity disorder, with a prevalence of 5% in children under 18 years of age, and dementias, which have a prevalence of 5.8% in those over 60 years of age. With the exception of substance use disorders and mental retardation, there are no notable cultural or national variations.

The burden of mental illness is immense, due to the functional disability it causes. It is estimated that 30.1% of the total burden of disease expressed in DALYs corresponds to neuropsychiatric disorders. The most relevant entities in this regard are depression (7.2%), dementia (3.7%) and alcoholism (3.4%). Although many sources, in different countries, reported increases in sick leave, early retirement and treatment rates due to mental disorders, rates in the community did not tend to increase in the pre-pandemic era, with some exceptions (e.g., the rate of dementia, related to population aging).

There is no doubt that the COVID-19 pandemic has had a negative impact on the mental health of the population, as it could not be otherwise. In this regard, a large number of "ad hoc" papers, based on cross-sectional Internet-based surveys of convenience samples, have reported that respondents were stressed, insomniac, anxious, and depressed [6]. This information is valuable because of its immediacy, but the most reliable data come from longitudinal studies with onset prior to the pandemic, allowing the impact of the pandemic to be assessed.

These studies indicate that the first phase of the pandemic, with the associated confinement, produced a clinically measurable increase in levels of psychological stress, as well as in anxious and depressive symptoms [7,8]. However, these levels were generally reduced after 6 months, although there is great heterogeneity in the magnitude of this improvement. [9,10]. Regarding the first phase, those most affected were young people under 35 years of age, women, and people living with children. As for the population sector with a more prolonged affectation, people with pre-existing mental disorders, disability or in socioeconomically disadvantaged social situations showed worse long-term resilience [11]. Nevertheless, and given that the effects of the pandemic are still lingering, it is still too early to make a full analysis of its impact on mental health.

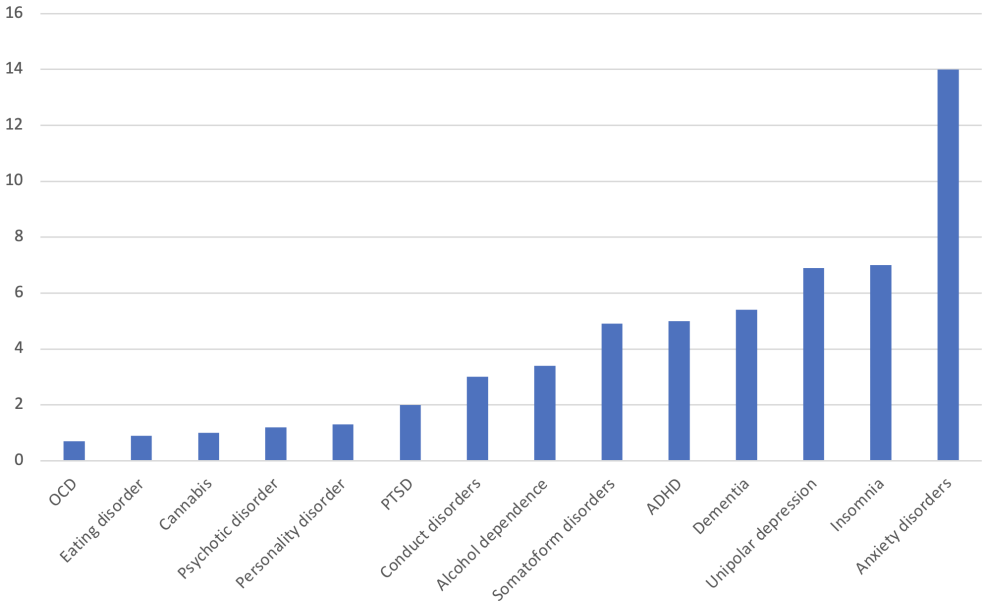

Figure 2 Annual prevalence (%) of mental disorders in Europe (Adapted from reference [5])

OCD: Obsessive-compulsive disorder; PTSD: Post-traumatic stress disorder; ADHD: attention deficit hyperactivity disorders

In Europe, mental disorders are the second leading cause of non-communicable diseases and account for 15% of the burden associated with disability (in terms of years lived with disability - YLD). In total, 16.9 million YLD occur (Figure 3).

Conclusions:

The most prevalent mental disorders in the community are anxiety disorders, sleep disorders and affective disorders, mainly depression. The COVID-19 pandemic has negatively affected mental health, especially in the first phase of the pandemic, coinciding with the situation of confinement. The clinical manifestations were mainly depressive, anxious and stress symptoms. Long-term effects appear to be minor, but studies are still needed to clarify this issue.

WHAT DATA DO WE HAVE ON MENTAL ILLNESS DURING THE COVID-19 PANDEMIC IN THE WORLD? WHAT HAS BEEN THE SITUATION IN SPAIN?

The impact of the COVID-19 pandemic on mental health has been studied from different perspectives. The first studies published, based on data from previous pandemics, warned about the potential impact of confinement on the increase of symptoms such as irritability, low mood, insomnia or post-traumatic symptoms, highlighting the usefulness of strategies such as altruism to counteract them [12]. Subsequent studies, with data collected during the COVID-19 pandemic, have confirmed the effect of confinement on mental health, with increased anxiety (OR = 2.79; 95%, CI: 1.467-5.324) and depression (OR = 2.0; 95%, CI: 0.883-4.527), identifying as risk factors the presence of psychosocial vulnerability, previous mental illness and longer duration of confinement [13].

Several meta-analyses have identified high prevalence rates of depression, anxiety, insomnia or distress [13-15] coinciding with the pandemic. A meta-analysis that included 48 studies with data representative of the general population and with pre- and post-pandemic data estimated a 27.6% increase in cases of major depression and a 25.6% increase in cases of anxiety disorders globally by 2020, with the greatest impact in those regions where the impact of COVID-19 was greatest [14]. In a study of 55,589 participants from 40 countries who completed an anonymous online questionnaire between April 2020 and March 2021, the percentages were lower than in previous studies, with probable depression detected in 17.8% and distress in 16.71% [16]. However, the risk of depression was higher in participants with a previous history of mental health problems (31.82% vs. 13.07%), being the risk higher for people with bipolar disorder and self-harm (RR= 5.88) and no increase in suicidal symptoms was detected in those with no previous metal disorder [16].

One of the populations that have been studied as particularly vulnerable is persons who have contracted COVID-19. The largest 2-year follow-up study, which included 1,487,712 patients with COVID-19, showed, compared with other respiratory infections, a transient increased risk of depression and anxiety during the first few months with subsequent decline and increased risk of cognitive fog, dementia, or psychotic disorders that was maintained after 2 years of follow-up [17]. In

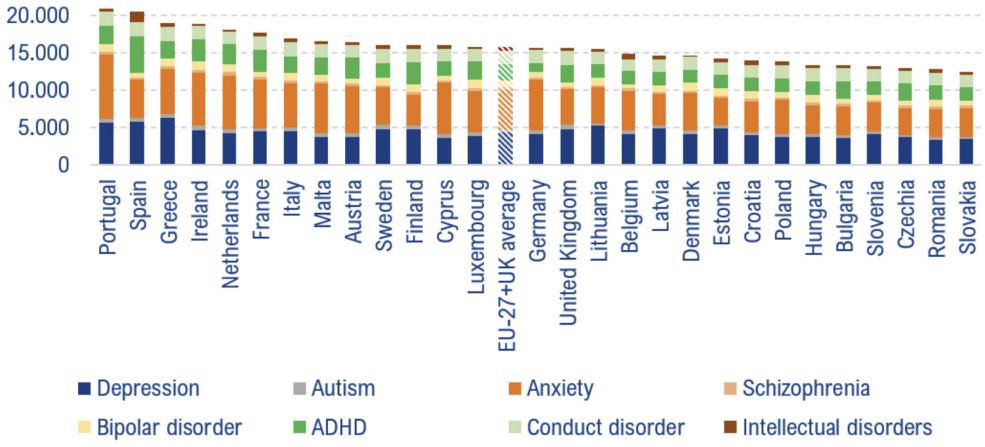

Figure 3 | **Prevalence of mental disorders in Europe per 100,000 inhabitants.**

children, the pattern differed, with no increased risk of anxiety or depression, but increased cognitive deficits, insomnia or psychotic disorders were detected, in addition to other neurological alterations at 6 months of follow-up. Interestingly, these results were similar regardless of the predominant COVID-19 variants [17]. From the previous data, it is inferred that people with previous mental health problems and those who have contracted COVID are population groups in which diagnostic and intervention strategies should be implemented given their higher risk of psychopathology.

Spain has been one of the countries most affected by COVID in the early stages of the pandemic. For example, in Madrid it was necessary to convert 60% of psychiatric hospital beds and reduce by 75% the number of professionals attending psychiatric emergencies in order to attend patients with COVID-19 [18]. Regarding the effect on mental health, in general, the results are in line with those previously reported. A recent meta-analysis, including 28 studies with 38 individual samples and more than 82,000 participants (including general population, students and healthcare workers) found prevalences of anxiety symptoms of 20% (95% CI: 15-25%), of depressive symptoms of 22% (95% CI: 18-28%) and of insomnia symptoms of 57% (95% CI: 48-66%) [15]. A study conducted in Catalonia, after the first wave (between May and October 2020), coinciding with the beginning of the lifting of activity restrictions, involving more than 9,500 people from a cohort representative of the general population, found higher prevalence of anxiety and depression in people with previous mental disorders (37.8% vs 10.1% and 25.4% vs 4.9% respectively), with living alone being a predictor of major depression in people with previous mental disorder (RR = 1.6; 95%, CI: 1.2-2.2) and the presence of interpersonal conflict and lack of financial stability predictors of mental disorder in those with no previous history [19]. These data contrast with primary care data, which document an initial increase in anxiety diagnoses, with a subsequent decrease, and a lower than expected rate of depression diagnoses throughout the pandemic [20].

Conclusions:

The COVID-19 pandemic has had an impact on the mental health of the population, reflected above all in an increase in cases of anxiety and depression. In people with previous mental health problems and in those who have had COVID-19 infection, the impact has been greater. The results of studies carried out in Spain have yielded similar results. There is still little data on the medium-term consequences of the pandemic, especially in vulnerable populations, to prepare for future needs.

IS IT TRUE THAT THERE IS A SIGNIFICANT DEVIATION IN THE INCIDENCE OF SUICIDE? HAS IT HAD A PARTICULAR IMPACT ON THE ELDERLY POPULATION? WHAT INTERVENTIONS HAVE BEEN MADE? BY WHOM?

There is little data on the association between pandemics and suicides [21]. Suicides are preventable and require early detection, awareness and interventions adapted to sociocultural circumstances [22,23].

From the onset of the pandemic, experts predicted a "prefect storm" with an increase in suicidal behavior in the general population [24,25]. However, the data from the first months did not confirm the increase in suicidal behavior, and in many countries suicidal behavior even decreased during the months of isolation. On the contrary, after those first months,

we have witnessed a very significant increase in suicidal behavior, especially in the form of attempts in young women in whom, according to data from the Catalan Suicide Risk Code, suicidal behavior has increased threefold, coinciding with the last months of mobility limitations due to COVID-19. In consummated suicides we only have the INE 2020 data, a year in which in Spain we beat the historical records of consummated suicides, with this increase being especially important in men over 70 years of age [26,27].

Unfortunately, the bad data on the increase of suicidal behavior in young people still persist. In 2022, and in the absence of INE 2021/22 data, everything points to the fact that the economic crisis resulting from the Pandemic and the war in Ukraine will lead to an increase in the suicide rate.

Contrary to the above, a study in Canada investigated the potential impact of the pandemic on adult suicidal ideation. To do so, they compared self-reported suicidal ideation in 2020 versus 2019. The percentage of adults reporting suicidal ideation since the onset of the pandemic (2.44%) was not significantly different from the percentage reporting suicidal ideation in the past 12 months in 2019 (2.73%) [28].

Conclusions:

The data available to us confirm the increase in suicidal behavior during the pandemic, according to INE 2020 data. The increase in deaths by suicide has been especially important in men over 70 years of age. The records of suicidal behavior (ideation + attempt confirm an increase especially in young women.

WHAT LESSONS HAVE WE LEARNED FOR THE FUTURE REGARDING MENTAL HEALTH? WHAT WOULD BE AVOIDABLE?

The COVID-19 pandemic has been unexpected, sudden and globalized in a very short time, forcing exceptional measures to be taken in a very short period, which have also affected mental health services. A study developed by the United Nations with data from 130 countries revealed an interruption in critical mental health services in 93% of the countries, highlighting the interruption in more than 60% of them for vulnerable populations and in more than 30% of emergency services or access to medication [29].

Adapting mental health systems to the pandemic has required combining infection control measures and changes in mental health access with the emergence of new needs [30]. This has meant, initially, reorganizing care, prioritizing COVID cases over psychiatric cases (reducing the number of beds available for psychiatry and, therefore, the average length of admissions in order to meet the demand with a limited capacity for care) and reassigning psychiatry professionals to other activities such as assistance to healthcare personnel or communication with the families of patients admitted or died of COVID-19 [31]. One of the main priorities has been to maintain care for patients with severe mental disorders or disabilities, especially difficult in a context of closure of intermediate resources such as day hospitals, day centers or rehabilitation units, and to facilitate the dispensing of medication.

The difficulty of access to healthcare centers and the need to maintain follow-up, especially for the most vulnerable patients, have led to the development of new modalities of care in record time. One example is telemedicine which, despite being available previously, has made significant progress, minimizing previous barriers, including technological barriers, barriers related to privacy and security, and barriers related to the perception of clinicians and users [30]. The experience generated has made it possible to see the possibilities that telemedicine can offer at the care level and to consider its implementation as an opportunity for the development of new care modalities, bearing in mind, however, that it should not replace face-to-face treatments when these are necessary and considering the difficulties of access for some populations. Together with telemedicine, the development of home hospitalization programs or new forms of integrated care in the community, the facilitation of online prescriptions or the use of digital medicine to carry out screening and differential diagnosis processes are other strategies that have begun to be developed [30].

The response capacity of the health system during the pandemic has been unequal, with populations with the most disadvantaged socioeconomic profile experiencing the greatest impact on their mental health [13]. As an example, the closure of educational centers and the loss of opportunities not only academic but also of socialization that it has entailed, has had a special impact on children in more vulnerable evolutionary situations (pre and adolescence) and on those with previously compromised socialization capacity, such as children with disabilities [32]. The impact on healthcare and frontline professionals has been particularly relevant, being one of the areas of action that have been prioritized at the height of the pandemic by mental health systems, highlighting the need for health systems to put prevention and attention to the mental health problems of their workers at the center of the pandemic [30]. The limitations in the possibilities of assistance from primary care during the pandemic have been an added factor whose impact on the health system and mental health in particular must be evaluated.

Conclusions:

Mental health has been severely affected during the pandemic, particularly in the most vulnerable. Mental health systems in the future will have to be more flexible and adapt to the needs of the moment, prioritizing the most severe cases and ensuring care for the most vulnerable.

The integration of research into care, the implementation of care quality indicators and the inclusion of users in the design of new services and their evaluation are necessary.

WHAT HAS BEEN THE IMPACT OF THE PANDEMIC ON THE MENTAL HEALTH OF THE ADOLESCENT POPULATION?

During the last two years, children and adolescents have been exposed to unprecedented events: confinement to their homes, school closures, reduced social interaction, fear of infection for themselves or their families, loss of loved ones, and uncertainty in their lives. Restrictions have had a particular impact on adolescents, who, due to their vital stage, need relationships with peers for their development and for the promotion of socialization and future autonomy.

Numerous risk factors have contributed to the deterioration of mental health in this population. These include the existence of a previous mental health problem or belonging to a vulnerable population subgroup (physical disability, minority groups). Regarding family factors, high parental stress has been observed in households with previous family conflicts, single-parent households, low-income families and families with children with special educational needs. Community factors include less access and social contact, especially with peers. All the aforementioned adverse factors can have a cumulative effect on the deterioration of adolescent mental health. In any case, it should not be forgotten that the family has been an important protective factor: greater closeness and communication with parents and the existence of structured routines, limited screen time, less exposure to news about the pandemic and adequate sleep schedules during confinement have been related to less psychopathology throughout the pandemic [33].

While there are a number of studies on child and adolescent mental health throughout the pandemic, findings have sometimes been inconsistent due to variability in the timing of assessment, the use of parent assessments, different restrictions in different countries, or different social contexts. There are two systematic reviews on the impact of COVID-19 on mental health in this population. The first one, conducted on the impact of confinement (61 articles including 54,999 children and adolescents), is a systematic review of the impact of COVID-19 on the mental health of this population [34], reports that confinement caused isolation and loneliness, irritability and anger, boredom and fear, and anxious and depressive symptoms in the adolescents. In addition, some previous disorders were exacerbated during this time, such as eating disorders, in which there may have been less monitoring of weight and food-related behaviors. Finally, a greater exposure to the Internet and social networks was observed, which was related to an increase in anxiety.

Another systematic review on mental health changes in children and young adults during the pandemic included 21 studies conducted in 11 countries on a total of 96,000 subjects aged less than 24 years [35], refers to a progressive deterioration in mental health, mainly in adolescents and young adults. An increase in the levels of anxiety, depression and psychological stress, an increase in negative affect, and the existence of greater isolation and feelings of loneliness during the pandemic are observed. The fact of a greater worsening in older adolescents may be due to the greater need for social contact and interpersonal relationships at these ages. On the other hand, a greater deterioration of mental health has been observed in girls, probably due to the increase in depression and anxiety during puberty and to the worsening of eating disorders, not only during confinement but throughout the pandemic. On the other hand, a decrease in the use of mental health services has been observed, especially in the early phases of the pandemic. Unfortunately, many of these studies are not longitudinal, so it is difficult to establish differences by age group, gender, or between different cultures or health policies.

Finally, it should be noted that the pandemic has led to a rapid change in the use of health care services, with an increase in telemedicine. Sometimes the lack of privacy or the difficulty of means in families with lower economic means have hindered its use, and it has been more successful for adults than for adolescents. For this reason, throughout the pandemic, there has been a tendency, as far as possible, to return to face-to-face care. On the other hand, interventions have been developed aimed at improving anxious and depressive symptoms and other related and relevant problems to treat such as negative affect, emotion management, intolerance to uncertainty, feelings of loneliness and problems with peers. An important aspect will be to transfer specific interventions for mental health care in this population to other areas such as schools and primary care [36], in addition to those already carried out in the specific mental health care centers.

Conclusions:

The COVID-19 pandemic has had particularly negative effects on the mental health of adolescents, especially in those who were previously vulnerable, especially those who already had some previous mental health pathology. Both during confinement and throughout the pandemic, there has been an increase in social isolation and symptoms of anxiety and depression. The pandemic has mainly affected adolescent women, with a notable increase in eating disorders.

HOW HAS THE PANDEMIC INFLUENCED DRUG ADDICTION AND OTHER ADDICTIONS (SOCIAL NETWORKS, VIDEO GAMES, COMPULSIVE SHOPPING, PORNOGRAPHY)?

The impact of the COVID pandemic on substance addictions and other non-substance addictions (social networks, video games, compulsive shopping, pornography) has been clearly demonstrated [37].

There has been a trend in the general population toward increased alcohol consumption during the pandemic. The proportion of people who consumed alcohol during the pandemic ranged from 21.7% to 72.9% and those who consumed other substances ranged from 3.5% to 17.5% in general population samples [38]. Risk factors for increased alcohol consumption were loneliness, male gender, older age, higher levels of educa-

tion, loss of income, unemployment, poor physical health (overweight), and previous mental health disorders such as fear, anxiety, impulsivity, depression, anxiety and hopelessness [39].

Cannabis and nicotine use showed increasing trends, as did cocaine use, while MDMA (ecstasy) use showed a decrease [40].

Periodic analyses of wastewater in European cities suggest that the use of most drugs has been lower during the initial confinements, but was subsequently recovering. A comparison with 2019 showed similar overall use of most drugs with the exception of MDMA and methamphetamine, two drugs for which the levels observed in 2020 were lower in most of the participating cities [41].

According to the European Monitoring Centre for Drugs and Drug Addiction (EUMC) [41], "the drug market was remarkably resilient to the disruption caused by the pandemic". Drug trafficking adapted to the new conditions with changes in trafficking routes and methods, further enhancing the digital presence of the drug market.... ". Any reduction in consumption observed during the initial confinements quickly disappeared as social distancing measures were relaxed. Overall, there appears to have been less consumer interest in drugs generally associated with recreational events, such as MDMA, and more interest in those associated with home use. However, "the easing of restrictions over the summer was associated with an uptick in use levels." In addition, "survey data suggest that those who used drugs occasionally before COVID-19 may have reduced or even stopped using during the pandemic, but more regular users may have increased their use..."[42].

As for non-substance or behavioral addictions, we will review some of them:

Gambling:

Regarding gambling, one of the consequences of the global restrictions by COVID-19 was the closure of urban premises (gambling halls, bingos and casinos) and the cancellation of sporting events. Despite this, gambling did not decrease in popularity and, in fact, the supply of online gambling increased, which led most countries to establish a series of restrictions and recommendations (United Kingdom, Portugal, Spain, Australia). Studies using data obtained from large online gambling operators in Europe confirmed that during the pandemic there was a significant decrease in gambling expenditure [43].

Pornography:

Pornhub web, porn world leader, reported an increase in pornography use in several countries, with overall traffic increasing by more than 11% from the end of February through March 17, 2020. Even countries without easy access to the Internet also reported increases in the range of 4 to 24%. In addition, searches for pornography with the terms "coronavirus", "corona" and "covid" reached more than 9.1 million. These data may give insight into how people may cope with forced confinement, stress and/or free access to pornography. Circumstances related to the COVID-19 pandemic may also limit casual sex and other behaviors, so people may use pornography as a coping strategy [44].

Compulsive Buying:

Compulsive shoppers often have unmanageable debts, which creates financial and emotional problems for them and their families. Therefore, compulsive buying, rather than excessive spending, is considered a repetitive and uncontrollable behavior, usually triggered by negative emotional states, where short-term positive rewards reinforce the behavior and lead to delayed negative consequences. Such rewarding, compulsive buying behavior has been observed among survivors of natural disasters, such as Hurricane Katrina and COVID-19. In the United States, in the six months following the onset of the pandemic, online impulse buying increased, especially after government financial assistance and among people who had more money to spend. Therefore, the most important determinant of compulsive buying was economic position [45].

Video games:

The confinement and quarantines of the coronavirus pandemic (COVID-19) generated greater involvement in online gaming. Initiatives such as "PlayApartTogether" that promote gaming to socialize and reduce stress attempted to achieve positive results. Although gaming can be a healthy coping strategy for most, it can also present risks for some vulnerable individuals. Thus, periods of social isolation with technology-based activity pose the danger of entrenching unhealthy lifestyle patterns, making readjustment difficult once the COVID-19 crisis is over. Nevertheless, there was a 75% increase in online gaming activity coinciding with the initial confinements, and in countries such as Italy, a 70% increase in internet traffic related to Fortnite games was detected. Steam, a gaming distributor, reported more than 20 million concurrent active users, and live-streaming platforms YouTube Gaming and Twitch reported a 10% increase in viewership [46].

Social Networking:

During the pandemic, a significant increase in the use of social networks such as Facebook, Instagram, Twitter and TikTok was noted [47]. A statistically significant increase in the number of women following appearance-focused Instagram accounts was found. In addition, significant relationships were found between frequency of Instagram use and body dissatisfaction.

These data suggest that confinement has had an impact on social media use, and this may be related to an increased drive for thinness and risk of eating disorders among adolescent and young women [48].

Conclusions:

The pandemic increased alcohol abuse and nicotine, cannabis and cocaine use. The use of synthetic stimulants decreased during periods of confinement but increased again when restrictions were lifted.

Regarding non-substance or behavioral addictions during the pandemic, gambling was severely restricted. Pornography experienced a marked increase and there was an increase in compulsive buying. The increase in video game use above 70% cannot be considered entirely dysfunctional as it was largely an adaptive mode of leisure that was considered optimal in that situation.

The use of social networks during the pandemic made it possible to maintain social connectivity and avoid isolation, although among patients with body image disorders it was harmful.

CAN STRESS LEVELS BE OBJECTIFIED?

To answer this question, we must reflect on two issues: the concept of stress and its evaluation.

There are different conceptualizations of stress depending on the scientific discipline from which it is studied. This has consequences on its evaluation and on the results obtained. For medicine and clinical psychology, stress is an internal condition of the organism that appears as a response to a threatening situation. This concept is based on the "General Adaptation Syndrome" model proposed by Hans Selye, and is reflected in expressions such as "I feel stress". It is associated with the experience of anxiety. However, occupational health psychology adopts a psychosocial perspective of stress that incorporates the environmental conditions that trigger the stress response. Stress is defined as a perceived substantial imbalance between the demands of the environment and the individual's ability to respond under conditions where he or she perceives that failure to cope with the demands has significant negative consequences for him or her. Emphasis is placed on the characteristics of the environment and its appraisal by the individual versus the response of the organism from the clinical perspective. This concept is reflected in expressions such as "in my job there is a lot of stress". It is considered that an environment with high levels of stress can be successfully managed by some people in such a way that they will not experience high levels of anxiety despite perceiving stress, nor clinical symptoms.

Adopting one or the other perspective has implications on the assessment of stress and the results obtained. While the clinical perspective assesses symptoms in the individual, the psychosocial perspective will assess the individual's perception of demand and control of his or her environment. Therefore, the content of the assessment instruments will differ, as will the results offered. For example, the ISTAS21 [49] is an instrument for assessing work stress through the perception that workers have of their working conditions, while the STAI [50] assesses anxiety levels and the CESQT [51] assesses levels of burnout syndrome, a response to chronic job stress, but all three instruments are used for the assessment of job stress.

The usual way to assess stress is by interview and questionnaires or psychometric tests. The interview provides qualitative data that experts must interpret in order to diagnose whether stress is the cause of a health problem. In addition to this diagnosis, questionnaires make it possible to quantify the levels of stress perceived by a person, considering reference points obtained from one or more samples drawn from a population that represents the individual being evaluated, and whose scores on the questionnaire are distributed following the pattern of the normal curve. However, the questionnaires used must have been validated, that is, they must be valid and reliable. Considering validity, a questionnaire must have sufficient content validity, construct validity (factorial, convergent and discriminant) and predictive validity. In addition, there must be normative criteria or scales to interpret the scores and to be able to reliably classify the subjects who respond to the test at a certain level of stress. All these analyses should have been calculated with sufficiently large samples, representative of the population and selected with adequate methodological criteria [52].

So can objective determinations of the levels of stress experienced by an individual be provided? The answer is yes, with a high degree of probability, at least $p < 0.05$, and provided that certain requirements are met. At least: (a) agreement on the phenomenon we want to evaluate (cause vs. consequence), (b) that the construct being evaluated corresponds to the concept we want to evaluate (content validity), (c) if a test is applied, that it is valid and reliable, (d) that the scales or classification and diagnostic criteria have been obtained with samples of sufficiently large size and representative of the population from which the subjects to be evaluated come, (e) that the scales are up-to-date, and (f) that these scales can be applied and the results obtained can be interpreted.

However, in order to determine stress levels we encounter the problem that it is not a directly observable phenomenon. We must evaluate it indirectly through the observation of certain indicators that define stress (content and concurrent validity) and the responses offered by people in the evaluation process, so the degree of sincerity of their answers can be a handicap to objectively determine stress.

Conclusions:

Stress levels can be objectified with a high degree of probability. To do so, the different perspectives for conceptualizing stress (clinical vs. psychosocial) must be taken into account. These perspectives determine the assessment procedures and instruments used to evaluate it and may provide divergent data for the same subject or set of subjects. In addition, valid and reliable instruments should be used when assessing stress and should be applied by expert professionals who know how to use them and interpret the results. As a limitation to obtain objective determinations, it should be noted that it is necessary for people to be sincere in their answers to the assessment instruments.

WHAT HAS BEEN THE IMPACT OF THE COVID-19 PANDEMIC ON PEOPLE WITH AUTISM SPECTRUM DISORDERS (ASD)?

The main symptoms of autism spectrum disorder (ASD) are

disturbances in social interaction and communication and the existence of repetitive and restrictive patterns of behavior and interests, and there may be other psychopathology in addition. Individuals with ASD and their families have particularly suffered adverse effects during the pandemic, especially during confinement. The abrupt closure resulted in decreased opportunities for social contact and interaction with peers, a fact of particular importance in this population. This increased social isolation and measures of social distance may have influenced the development and maintenance of social and communication skills and decreased emotional well-being in persons with ASD. In children, the symptoms of these disorders were clearly aggravated with an exacerbation of behavioral and emotional problems, fundamentally in children in whom these problems already existed previously [53]. In addition, it should not be forgotten that the affectation can be very different depending on the initial functioning of the patient, and on the existence or not of language. In our setting, a study evaluated the psychosocial status of children and adolescents with ASD in treatment in a specialized unit, during and after confinement, showing a worsening of the core symptomatology of ASD, an increase in the use of new technologies and the appearance of anxiety symptoms. This clinical and functional worsening caused an increase in the use of rescue medication mainly during confinement [54]. In the adult population, younger, female subjects with a previous diagnosis of another mental disorder had greater difficulty in coping with the effects of the pandemic [55]. However, it should also be considered that the fact that social demands were reduced during the pandemic may have benefited subjects with ASD, mainly adults, by improving their symptoms [56].

Worsening of typical ASD symptoms and added psychopathology has been associated with increased levels of parental stress. Throughout the pandemic families have experienced high levels of caregiver burden, anxiety and increased family conflict. These levels of parental stress have been associated with younger age of children with ASD. It has also been noted that the worsening of the disorder is less in families with good emotional support and high capacity to adapt to changes [57].

On the other hand, parents have reported a loss of institutional care support. In children and adolescents, the closure of schools, which play an important socialization role as well as providing structure and routines, and the lack of access to therapeutic interventions, have introduced significant stress, especially important in children with special educational needs. The disruption of routines and unpredictability due to the pandemic has increased parental concerns and led to increased care needs of the ASD population. The need for careful planning of time structuring and organization and the use of emotional regulation strategies in this population should be noted.

Finally, it should be noted that one of the negative effects of the pandemic has been the waiting list in health care facilities for the possible diagnosis and treatment of this disorder. Thus, the need for alternative strategies for diagnostic evaluations and therapeutic interventions has become evident. At the therapeutic level, experiences have been studied using telemedicine that have proved effective in the treatment of these patients in pandemic situations [58]. At this point, we cannot forget the families with fewer resources, which usually have a greater intrafamily burden and a higher need for visits, and should be provided with easy access to diagnostic and treatment services.

Conclusions:

During the pandemic, the problems of patients with autism spectrum disorders have increased. Both the main symptoms of the disorder have worsened and there has been the appearance of significant stress in parents and caregivers.

PART TWO: IMPACT OF THE PANDEMIC ON THE MENTAL HEALTH OF HEALTH CARE WORKERS

WHAT WERE THE MENTAL HEALTH DISORDERS SUFFERED BY HEALTH CARE WORKERS, AND WERE THERE SIGNIFICANT DIFFERENCES WITH THOSE OF THE GENERAL POPULATION?

Although many of the studies conducted on mental health in health care workers have serious methodological limitations as they tend to be based on voluntary surveys rather than epidemiological studies with systematic evaluations, they all confirm that during the pandemic health care workers were exposed to a high level of stress and suffered significant mental health problems.

Data from a US national survey of voluntary, self-selected health care workers showed in a series of 1,685 participants that almost half of the health care workers reported severe psychiatric symptoms, including suicidal ideation, during the COVID-19 pandemic. Thirty-one percent of them had mild anxiety, 33% clinically significant anxiety, 29% mild depressive symptoms, and 17% moderate to severe depressive symptoms. Suicidal ideation was reported by 5% of the participants [59].

In a meta-analysis on the impact on the mental health of healthcare workers, a search of 18,609 articles was undertaken, of which 44 were chosen for the final analysis and 29 were subjected to meta-analysis. Insomnia, anxiety, depression, Post Traumatic Stress Disorder (PTSD) and stress were some of the psychological problems faced by healthcare workers. Overall, the joint prevalence of these mental health problems was higher among physicians, nurses, and older staff in the subgroup analysis [60].

In Spain, the MINDCOVID study, financed by the ISCIII, carried out a survey involving more than 9,000 professionals [61]. According to this study, up to 45% of the people surveyed were at risk of having mental illnesses, the most frequent being depression, anxiety disorders, post-traumatic stress disorder and substance abuse. The study data confirmed that the main risk factor for mental illness was a history of previous mental disorders and that the prevalence data was almost double that of the general population. Follow-up data from

this study confirm the high prevalence of risk and persistence of mental disorders in professionals who presented with them in the early stages.

Conclusions:

The available data confirm the increased risk of mental illness to which health professionals were exposed during the early phases of the pandemic, a risk that seems to persist in many professionals at the present time.

WHAT HAVE BEEN THE RISK FACTORS FOR SUFFERING FROM ONE OF THESE DISORDERS?

Psychological distress was generally associated with female sex and younger age. Within professional categories, it appears that nurses suffered greater psychological distress, particularly if they worked on the front line, compared to other professionals with less direct contact with patients or infected persons [62,63].

Among the risk factors for developing depression, previous presence of a poor mental health status or the presence of pre-existing organic diseases, female sex, working in a secondary hospital and being on the front line having direct contact with infected persons have been found to be the most evident risk factors [64].

On the other hand, living in rural areas, having contact with COVID-infected patients and the presence of organic diseases were associated with obsessive-compulsive symptoms in healthcare workers.

Finally, not being able to access therapeutic or preventive interventions in times of need and barriers to the implementation of such interventions also had a negative impact on the mental health of professionals. Lack of equipment or staff time or lack of skills needed to provide supportive interventions for frontline workers were among those barriers that prevented workers from getting the help they needed to cope with the pandemic [65].

Some geographic differences were found, although not for all conditions assessed. Specifically, a higher prevalence of PTSD symptoms was found in professionals working in North America than in Asia.

Conclusions:

The literature suggests that there were several risk factors for various mental health disorders during the pandemic. Female sex, being a nurse, proximity to patients with COVID-19, exercising in a rural setting, and having previous psychiatric or organic illnesses were some of the most frequently repeated factors in various studies.

HAVE THESE MANIFESTATIONS BEEN UNIFORM THROUGHOUT ALL WAVES OF THE PANDEMIC?

There have been changes in the mental health of workers throughout the waves of the pandemic and there are several factors that could explain some of these changes [34,62,63].

In the first wave of the pandemic, healthcare workers, as well as the rest of the general population, faced a new threat, with more questions than answers and with a lot of inconclusive (if not contradictory or low quality) information in the media. The fear of the unknown had a great impact and, in general, the response was one of rapid adaptation to what was happening, and in most cases both healthcare professionals and the general population complied with the different regulations that were being established by the public administrations.

During the first wave, different coping mechanisms were activated at the psychological level by the general population and health professionals, who in many cases showed enormous levels of resilience and adaptive capacity. However, these mechanisms, in some cases, were depleted and were not sustainable in the medium or long term, resulting in the emergence of mental health problems. For example, the impact of confinement measures on the mental health of individuals, including health professionals and their families, has been found to be greater in the subsequent waves of the pandemic compared to the first wave. Economic and social problems associated with the pandemic also had a greater impact across waves and were associated with mental health problems.

It should be noted that health care workers received many expressions of support and affection during the first wave of the pandemic. Many people took to the streets and balconies to thank health professionals for the work they were doing. Although they did not disappear, the number of assaults on health workers decreased in some countries and there was a general atmosphere of respect and appreciation for the work of health workers. Over the following waves, these signs of support diminished and generally returned to previous levels. It should also be borne in mind, as mentioned above, that many people were already observing a decline in their ability to adapt.

Finally, the changes in the morbidity and mortality of the virus along the different variants should be noted. Initially, there was an under-diagnosis of infected persons worldwide, which prevented us from knowing exactly what the morbidity and mortality of COVID-19 was, since the data were mainly from persons who were admitted to hospital. Following the emergence of variants with higher morbidity and mortality, COVID-19 mutated and began to replicate more in the upper respiratory tract, which decreased mortality and the need for hospitalization in infected individuals. This has led to a relaxation in protective measures, and also to less fear and thus a potential reduction in acute mental health problems. This trend, however, has not been observed in mental health disorders and chronic mental health problems, which continue to appear.

Conclusions:

Mental health alterations in healthcare workers have not been the same in the different waves of the pandemic. In the first wave, the response was one of rapid adap-

tation to what was happening, activating different coping mechanisms at the psychological level that showed enormous levels of resilience and adaptive capacity. Mental health disorders in healthcare professionals have been higher in subsequent waves.

IN WHAT WAY, AND TO WHAT EXTENT, HAS THE PANDEMIC INFLUENCED THE BURNOUT SITUATION OF HEALTHCARE WORKERS?

As noted in the webinar "Burnout in Spanish physicians. Before and after the pandemic", published by the Health Sciences Foundation in June 2020, healthcare workers saw how some of their working conditions deteriorated dramatically and how several professional demands that induced work stress were increased [66]. It was pointed out in that webinar that these included emotional demands and emotional labor, work overload, exposure to risks and hazards, lack of social support at work, and perceived lack of organizational justice and lack of social justice.

The change that induced this deterioration in working conditions occurred suddenly, in a very short period of time, so that people activated coping strategies to manage the new demands and their consequences. The result was embodied in responses derived from exposure to high levels of acute work stress, namely: physical exhaustion, emotional exhaustion, compassion fatigue, feelings of helplessness and vulnerability, fear and distress, and perceived abandonment and indifference on the part of the organization for which they worked. But at that time, burnout did not increase as a health problem resulting from the new working conditions.

It was also advanced in that webinar that the increase in the levels of burnout would come later, past the time of acute work-related stress, as it is a response to chronic work-related stress that has not been successfully managed. It is from 2022 onwards that we would expect to see a clearer increase in the levels of prevalence of burnout as a result of chronic exposure to these deteriorated working conditions, which have not changed after the exposure of professionals to successive waves of increase in the number of infections with health care demand and hospitalizations.

However, an exponential increase is not to be expected in the immediate future. People have coping strategies to manage stress and prevent health problems, and it is to be expected that most professionals working in healthcare will manage the new working conditions for a while, either through personal resources or, in the case of stress responses, by enlisting the help of healthcare professionals. It is also to be hoped that governments and organizations will react in time to avoid a collapse of the healthcare system. Empirical studies conducted in the USA on medical professionals show mixed results. Some studies show an increase in burnout levels between 2020 and 2021, but with non-significant differences [67]. In others, the levels are increased (e.g., 2018 = 40%, 2021 = 61%), but no statistical tests are performed to assess whether the change is significant [68]. And there are studies that conclude that burnout levels improve in 2020/2021 when compared to those obtained in 2017 [69].

Interesting are the results of the annual studies conducted by the Medscape organization on U.S. physicians [70]. Shows that in 2021 a rebound in the percentages of burnout cases begins, although this increase does not reach the values obtained in 2016 and 2017.

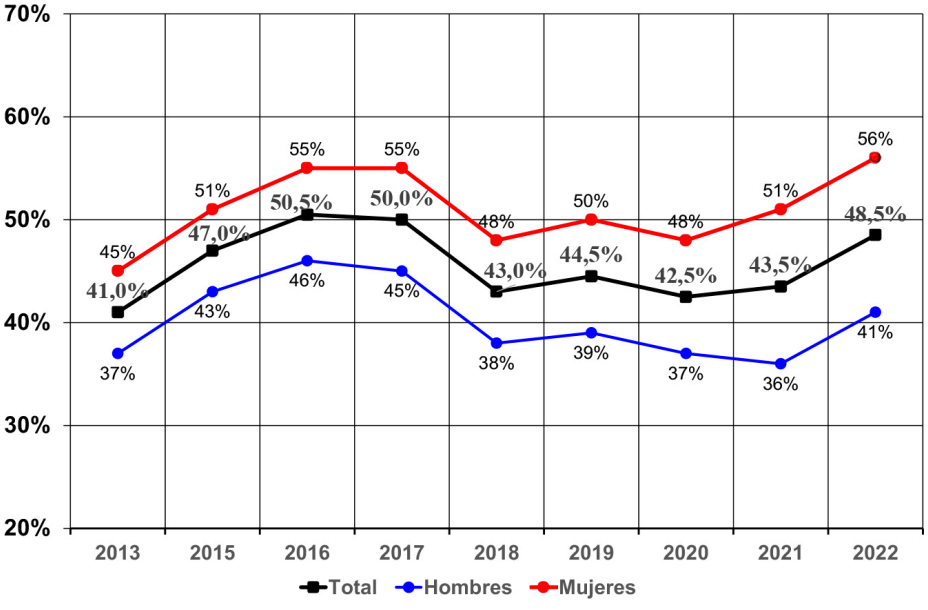

Figure 4 | **Annual trend of burnout percentages in U.S. physicians (Medscape annual series).**

In the case of nursing professionals the results presented by Medscape in 2021 [71] also indicate an increase, from 12% of participants with high and very high levels of burnout in the registered nurse group before the pandemic to 37% after the pandemic. In Spain, the studies, with smaller and more specific samples than those of the USA, show a significant increase in the levels of burnout evaluated before, during and after the first waves of the pandemic [72].

The disparity of the results may be influenced by variables such as the geographical area where the study was conducted, the size and composition of the sample, the instrument used to collect data and the criteria used to identify levels of burnout.

Conclusions:

As defined by WHO in ICD-11, burnout is the result of chronic stress in the workplace that has not been successfully managed. For this reason, during the first waves of the pandemic, no increase in its prevalence was observed. However, prevalence studies now indicate a slight increase in the levels of burnout in healthcare workers. Nevertheless, it is to be hoped that the ability of professionals to adapt and cope with the stressful work environment together with the reaction of governments and the management of healthcare organizations to modify working conditions will prevent such an increase. The differences observed in the results of the studies may be influenced by the procedure used to carry out the study (e.g., characteristics of the sample and questionnaire used for data collection).

WHAT HAVE BEEN THE MENTAL DISORDERS AFTER COVID IN HEALTHCARE WORKERS?

The development of mental disorders in healthcare workers as a consequence of patient care in the context of epidemic outbreaks caused by new microbiological agents has been previously described, with the SARS epidemic of 2003 and the Ebola outbreak of 2014 being examples of the impact that these situations can have on the mental health of healthcare workers in the front line of patient care.

These epidemic outbreaks share similar risk factors such as: high workloads, the need to perform medical activity under uncomfortable protective equipment and the fear of both contracting the disease and transmitting it to family members and cohabitants. All these circumstances can have a severe impact on the mental health of these workers, with the possibility of post-traumatic stress disorder, depression and substance abuse [73]. Sometimes, these pictures appear on previous mental disorders being health care a profession with significant suicide rates [74].

The SARS-CoV-2 pandemic has had a significant impact on the mental health of healthcare workers, with depression, anxiety and post-traumatic stress being the most prevalent clinical conditions. A meta-analysis of 65 studies involving almost 98,000 healthcare professionals from several continents estimates a prevalence of 21.7% for depression, 22.1% for anxiety and 21.5% for post-traumatic stress disorder. This study only considered the three pathologies to be present if the symptomatology was at least moderate or if it was considered clinically relevant, thus excluding milder conditions that are likely to be less dysfunctional. These estimates are considerably high when compared with the general population, outside an epidemic context, which are around 3.5-4.5%, which shows the strong impact of epidemic conditions in the health population at the mental level [75].

The SARS-CoV-2 pandemic presents certain specific conditioning factors, mainly due to the high incidence of the disease worldwide and the associated health care collapse, which has led to situations such as the following in a generalized manner: the death of many patients unaccompanied by family members and healthcare workers, the need to wear protective suits making physical and sometimes verbal contact with patients impossible, the transmission of information to family members about the death or poor evolution of a patient by telephone rather than in physical presence, or the words of farewell from patients to their families by telematic means and in the presence of the healthcare worker. These situations described are commonly expressed by health care workers in the front line of care for these patients and exemplify the feelings of anxiety, frustration and abandonment sometimes reported by health care workers and which represent a high emotional burden [76].

A study analyzing the prevalence of post-traumatic stress at 8 months and carried out in Chinese health care workers (mainly nurses) in the first months of the pandemic identifies social isolation, the presence of chronic diseases and dissatisfaction with the job as risk factors. On the other hand, receiving adequate information on the characteristics of SARS-CoV-2 infection, having a good family structure and the development of clinical activity in adequately prepared structures appeared as protective factors [77]. A study of health care workers in France identified female gender, nursing profession, jobs considered to be of low rank and low levels of experience as risk factors [78].

Certain measures and interventions have shown efficacy in preserving the mental health of healthcare workers. Training in self-care of the professionals themselves is a first measure given that they often tend to prioritize patient care as they may consider dedicating time to self-care as a selfish attitude. Likewise, the normalization and recognition of mental disorders in this context in health professionals and the limitation of work time should be a priority.

The use of psychological counseling through telematic or face-to-face means, support groups or group therapy are considered beneficial by users, although some studies reflect the difficulties of access to these resources [79]. In a study evaluating healthcare workers in the United States, 20% of workers who felt they needed support or care for their mental health did not have access to these services and in those places where they were offered, only 11% attended and almost a third of workers were unaware that this care was offered by their facility [80].

Conclusions:

COVID-19 has had a relevant impact on the mental health of healthcare workers, with depression, anxiety and post-traumatic stress being the most frequently developed symptoms.

It is necessary to develop and implement preventive measures and psychological assistance to healthcare professionals to avoid or mitigate as far as possible the development of mental pathology associated with the exercise of their healthcare activity.

HOW DOES THE HEALTH AUTHORITY VIEW THIS PROBLEM?

The United Nations Inter-Agency Standing Committee on Humanitarian Assistance recommended from the outset that Mental Health and Psychosocial Support should be a central component of any Public Health response [81] and will be part of the comprehensive strategy aimed at preventing infections, saving lives and minimizing their effects as advised by WHO [82].

In Spain, the response was heterogeneous depending on the region. In the Community of Madrid, an early response was promoted through a Priority Mental Health Care Response Plan in the crisis by COVID19 [83] The regional COVID plan was implemented in May 2020, without any continuity with the previous and subsequent plans and following a path of investment maintained over time with the recruitment of professionals as a top priority. This autonomous COVID plan was conceived in line with the guidelines published by the United Nations in a specific document [84] and included the importance of mental health promotion from a population approach in post-crisis actions in different sectors. It also considered it necessary to cover emergency care for mental health and psychosocial problems. The third proposal of the United Nations document speaked of the opportunity to build a mental health care organization for the future, of quality, to support the recovery of society, which requires a specific investment, aimed at three focuses :1. Attention to health professionals. 2, Strengthening community services, and 3. User participation and first-person evaluation of the experience.

In the case of healthcare professionals, specific care is provided at the hospital, outpatient and primary care levels, with different approaches in the different pandemic phases. In addition, we have a pioneering and unique Program for the Integral Care of Sick Healthcare Professionals (PAIPSE) among the autonomous communities that works closely with the occupational risk services and has been reinforced from the outset with the increase of more than a third of its staff.

Returning to the general framework, neuropsychiatric diseases, which were previously at the forefront of the disease burden in Europe, acquire special relevance in the current post-pandemic context. Mental health is recognized as an area of high risk of affectation in all age groups, and especially in adolescents, young people, and vulnerable populations, making it essential to develop specific measures in addition to the usual ones to date.

We find ourselves in an unprecedented global scenario that may provide an opportunity to reverse the global historical gap that mental health problems are widespread, undertreated and under-resourced, as well as the gap between the estimation and allocation of resources to implement mental health plans [85].

Conclusions:

The United Nations Inter-Agency Standing Committee recommended from the outset that actions in Mental Health and Psychosocial Support should be a central component of any Public Health response. In Spain, the response was heterogeneous depending on the territories.

IS THE PRESS AWARE OF THIS ISSUE AND WHAT ROLE SHOULD IT PLAY?

The correct approach to mental health problems in the media is one of the main concerns of the board of the National Association of Health Informers (ANIS). For this reason, monographic congresses and specific presentations have been organized for the more than 600 communicators who are members of the association.

In addition, the association has collaborated with the Ministry of Health in the publication, in July 2020, of a document of recommendations for the media aimed at facilitating the approach to information on suicidal behavior and contributing to its prevention.

With regard to healthcare professionals, numerous reports and information have been published for years on the problems inherent in these professions with regard to mental health.

Initiatives such as PAIME have received wide coverage, especially in the specialized media. The impact of the pandemic on mental health and burnout has been one of the most emphasized aspects. And, from our point of view, the public's perception of this problem has been remarkable, especially during the confinement.

Conclusions:

The problem of mental health of both the general population and health care workers is known by the media who have organized monographic congresses on this subject.

WHAT REFLECTIONS FROM AN ETHICS PERSPECTIVE DO THE PANDEMIC-DRIVEN MENTAL HEALTH ISSUES IN THE GENERAL POPULATION AND IN HEALTHCARE WORKERS RAISE?

Classical psychiatry distinguished two types of factors in the production of mental disorders, which it called "endogenous" and "exogenous". Exogenous factors were environmental factors, therefore, external to the individual, which, by acting on him, ended up altering his psychic equilibrium. Endogenous factors, on the other hand, were characterized by being inter-

nal to the individual. In addition to this, they were traditionally considered unknown, although this has been changing as a result, above all, of advances in biochemistry and genetics. In classical psychiatry, this gave rise to the division of mental disorders into two major chapters, known as "psychoses" and "neuroses". It is true that psychoses included not only the so-called endogenous psychoses (schizophrenia, manic-depressive psychosis), but also others of exogenous cause, such as those produced by alcohol, drugs, certain microorganisms such as *Treponema pallidum*, or some heavy metals. But the psychoses par excellence were the endogenous ones. Exactly the opposite of what happened in neuroses, in which the cause of the disorder was always in conflict with some element coming from the environment.

The virus causing the current pandemic does not seem to produce psychiatric disorders per se, as was classic in the paradigmatic case of *Treponema pallidum* and progressive general paralysis. The current virus has not been proven to be the triggering cause of any major psychiatric disease, although, as we shall see immediately, this does not prevent it from contributing to the development of psychiatric disorder [17]. The fundamental disorders diagnosed throughout this pandemic belong rather to the field of what in classical terminology were called neuroses, disorders due to nosogenic factors of the environment that end up altering the mental equilibrium of people.

The COVID pandemic has significantly altered the living environment of human beings. It has forced rigorous confinement for months, disrupting family relationships as well as professional and work relationships. The consequence has been a very significant increase in the number of interpersonal conflicts. When the person was already a carrier of a latent predisposition to suffer from a mental disorder, this crisis has triggered it. Hence, it has also had an impact on the appearance of major psychiatric disorders. But above all, it has increased the number of interpersonal conflicts, triggering exaggerated or abnormal responses. This explains why cases of anxiety, depression, discomfort, self- and heteroaggressions, etc. have increased.

As was to be expected, these disorders have been all the more frequent the "weaker" people are. Situations of "crisis", and this pandemic has been to a high degree, test the so-called resilience mechanisms, affecting more the weaker personalities, or those who for different reasons are in a bad moment. This is fundamental to take into account. Crisis situations test the psychic strength of people and cause the weaker ones to fail in their response, so that they begin to show exaggerated or abnormal symptoms of discomfort, anxiety, insomnia, anguish, aggressiveness, etc. To help them overcome the situation, psychiatry uses two types of treatment, some pharmacological and others psychotherapeutic. The latter seek to re-educate the patient, strengthening his or her psyche and providing him or her with mechanisms for coping with crisis situations. These mechanisms, by improving the patient's relationship with his environment, will allow him to reduce his suffering and attenuate the effect of these life-altering symptoms.

What role can ethics play in this context, and can it be of any use?

A first important observation is that our relationship with the environment is conditioned by our own internal vitality. Ortega y Gasset tells us in a text entitled "Vitality, soul, spirit", how the level of our vitality is a determining factor in the way we face the environment. Ortega writes: "Who has not experienced it? When we separate from a certain person with whom we have been talking for a long time, we feel invigorated. And not because that person is very intelligent, nor because he has been kind: we owe him neither a teaching nor a favor. However, we come out of our dealings with that person refreshed, full of self-confidence, optimistic, saturated with impulses and plenitude, with a firm faith in existence. If we want to analyze the reasons for this corroboration and increase of vitality, we do not find any concrete one. But there are other people whose proximity, however brief it may be, leaves us battered and exhausted, full of mistrust and as if existence had taken on a sour taste. When we are separated from them, we are less than before and, so to speak, we have lost calories. Indeed, there are two kinds of beings: some are endowed with overflowing vitality, who remain in 'surplus'; others, with insufficient vitality, always in 'deficit'. The excess of the former contaminates us favorably, corroborates and nourishes us; the defect of the latter sips life from us, depresses and diminishes us." [86].

There are people with high vitality and people with low vitality. And, of course, there are also cases in which vitality, both high and low, acquires pathological overtones, as happens in manic and depressive disorders. But leaving aside these clearly pathological cases, it is clear that we all have what Zubiri called a "vital tone", and that this is very different in some situations and in others. The paradigmatic example of this is the current war in Ukraine. The Ukrainian soldiers are fighting for a cause they consider just and important, and therefore have a high "combat morale", while the Russian soldiers seem to be fighting for a cause they do not understand and which they find it difficult to assume as their own, or which they openly do not share. The former are demonstrating very high morale, while the latter seem to have their morale in the doldrums. It goes without saying that morale depends on many factors, one of which is education. One fights for ideas and ideals; if you prefer, for beliefs. This, which is so neglected in Western culture, is always fundamental, but especially in crisis situations. A demoralized people will be at the mercy of whichever wind blows the hardest, it will be a toy in the hands of anyone. And the same can be said of the demoralized person.

Hence the importance of morality, i.e. ethics. This is particularly clear in crisis situations. Ethics is the attempt to answer the question that every human being asks himself at some point in his life: "what should I do". Whoever is able to ask himself the question and has a clear answer, that is to say, who knows what he should do, it is very difficult for him not to carry it out with determination and conviction. And it is also very difficult for him to "burn out" or become depressed in the face of adverse circumstances. In this sense, ethics is a very

effective antidote against depression and discouragement, and against not all, but some of the disorders that Benjamin Rush and James Prichard baptized with the name of moral insanity, which French psychiatrists called "folie morale" and which in 19th century German psychiatry was known as "moralisches Irresein". In 19th century German ethics there was a term that played a very important role. It was "Gesinnung", a word that is difficult to translate, but which, among other possible meanings, has that of "disposition of mind". In Kantian ethics it is the fundamental element of the moral life of people.

The disposition of mind has an undoubted biological basis. Among us, López Ibor has dealt extensively with it [87]. But on that basis, let us say, biological or of first nature, there rises the one that we build with our acts, habits and ways of life, that is to say, what the classics called second nature. But not all acts and habits contribute to the same extent to the formation of the basic or fundamental dispositions of mind. The decisive ones are those that are learned, usually unconsciously, during the first stages of life. Hence, between the genetically determined traits and what is acquired in the course of life in contact with the environment, an intermediate space must be found, which German philosophers, especially from Kant onwards, designated with the word "Gesinnung". "Gesinnung" has to do not so much with concrete acts as with the "attitudes" that the human being learns during the first stages of his life, in the epoch of maximum cerebral plasticity, and which constitute the basis on which the different acts are later based. "Gesinnung", as the philosopher Max Scheler affirmed, consists in the "orientation" of one's own life [88] . It goes without saying that this topic goes far beyond the limits of this brief note. But it was important to bring it up in order to point out that the reactions of human beings, especially in crisis situations, are strongly conditioned, and even determined, not only by what was formerly called "temperament", and today "genetic information", but also by what in the old terminology was understood as "character". Temperament is "physical", whereas character has a large learned, and therefore "moral", component. Both are put to the test in crisis situations, such as the present one. The human response to crises is not only determined in people by their physical condition, that is, by their temperament, but also by their character, or by what Aranguren called their "disposition", which defines their moral condition. And this is, in my opinion, the great black hole of the current situation, how neglected is the formation of children and young people in this element, a determinant in much of the character of people and the functioning of societies. In their most deviant forms, these people make up the group of so-called psychopathies or sociopathies. But there remains the other large group of people, those considered "normal", possessing dispositions with very different degrees of resilience. It is crisis situations, such as the current one, that make this evident, and also destabilize the weakest or worst prepared.

Conclusions:

Crisis situations test people's resources, both physical (illnesses, disabilities, biological deficits) and moral (people's moral resilience, "high morals" and "low morals", etc.). Moral resources are acquired in education, in interaction with other human beings, and form the reservoir of people's values and beliefs. Crises trigger not only physical, but also moral claudications.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Etiología microbiana de la prostatitis crónica bacteriana: revisión sistemática

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RESUMEN

Objetivos. Recientemente se ha descrito la importancia de los microorganismos grampositivos y de las bacterias atípicas en la prostatitis crónica bacteriana (PCB). Por ello, en este estudio se analiza la etiología de la PCB, así como la evolución de la resistencia antibiótica a través de una revisión sistemática.

Material y métodos. Se ha realizado una revisión sistemática de estudios obtenidos a través de la base de datos MEDLINE (PubMed), relacionados con la etiología y el perfil de resistencia antibiótica de la PCB, publicados con anterioridad al 1 de julio de 2021.

Resultados. Los principales microorganismos aislados en los estudios incluidos en la revisión fueron *Enterococcus faecalis* (46,90%), *Staphylococcus* spp. (22,30%), *Escherichia coli* (15,09%) y bacterias atípicas (6,04%).

Conclusiones. La PCB está experimentando un cambio de paradigma, ya que las bacterias grampositivas y las atípicas se erigen como los principales agentes causales de esta entidad. Esto obliga a replantear la estrategia terapéutica utilizada, pues es necesario utilizar antibióticos que asuman el viraje etiológico y el perfil de resistencias antibióticas descrito.

Palabras clave: prostatitis crónica bacteriana; etiología; resistencia antibiótica

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Microbial etiology of bacterial chronic prostatitis: systematic review

ABSTRACT

Objectives. The importance of Gram-positive microorganisms and atypical bacteria in chronic bacterial prostatitis (CBP) has recently been described. For this reason, this study analyzes the etiology of CBP, as well as the evolution of antibiotic resistance through a systematic review.

Material and methods. A systematic review of studies obtained through the MEDLINE (PubMed) database, related to the etiology and antibiotic resistance profile of CBP, published up July 1, 2021.

Results: The most frequent isolated microorganisms that we have found in publications are *Enterococcus faecalis* (46.90%), *Staphylococcus* spp. (22.30%), *Escherichia coli* (15.09%) and atypical bacteria (6.04%).

Conclusions:. CBP is undergoing and unprecedented change of paradigm. Gram-positive bacteria and atypical bacteria are the main pathogens involved in the aetiology of this entity. This forces us to rethink the therapeutic strategy used, since it is necessary to use antibiotics that assume the etiological change and the profile of antibiotic resistance described.

Keywords: chronic bacterial prostatitis; aetiology; antibiotic resistance

INTRODUCCIÓN

La prostatitis crónica bacteriana (PCB) (Categoría II) se caracteriza por la aparición de síntomas obstructivos e irritativos del tracto urinario inferior, asociado a disfunción sexual e infección del tracto urinario de repetición [1]. Históricamente se aseguraba que el microorganismo más frecuente implicado en la PCB era *Escherichia coli* y otros bacilos aerobios gramnegativos [2,3], quedando los grampositivos en segundo lugar, no siendo posible en muchas ocasiones demostrar el papel patogénico de estos últimos.

Sin embargo, el concepto, etiopatogenia, clasificación y tratamiento se encuentran en pleno proceso de revolución y cambio. Se reconoce cada vez más el papel fundamental de las bacterias grampositivas y de las bacterias atípicas (*Ureplasma* spp., *Chlamydia trachomatis*, *Mycoplasma hominis*, etc.) como agentes directamente implicados en la etiología de esta entidad [4].

Todo ello debe conducir a una modificación en el protocolo de tratamiento de estos pacientes, siendo necesario encontrar una pauta terapéutica que asuma el viraje etiológico actual, conservando los principios de coste-beneficio y adherencia terapéutica, además de limitar el desarrollo de resistencia antibiótica [2].

Sin embargo, la escasez de publicaciones que lleven a cabo un análisis holístico y sistematizado de la etiología y resistencia antibiótica de la PCB resalta la importancia de este estudio. Esta entidad es bastante desconocida, siendo difícil diagnosticar y clasificar a los pacientes; esto ocasiona que los criterios de inclusión en los distintos ensayos sean diferentes, excluyéndose en una gran proporción de ellos a las bacterias atípicas, reconocidas ya como agentes implicados en la patogenia de esta entidad [4]. Por otra parte, la PCB es difícil de tratar, con una elevada tasa de recidivas y en la que los pacientes tienen una pésima calidad de vida [5]. Además, no existen estudios recientes que analicen la evolución de las resistencias antibióticas en un periodo de tiempo determinado. Por todo ello, nuestro estudio resulta de una enorme importancia para ayudar al entendimiento y tratamiento de esta entidad. En él, se analizan la etiología y evolución de la resistencia antibiótica en la PCB a través de una revisión sistemática.

MATERIAL Y MÉTODOS

Se han seguido las normas de PRISMA (https://prisma-statement.org//) para realizar esta revisión.

Fuentes de información y selección de estudios. Se realizó una búsqueda bibliográfica en la base de datos MEDLINE, a través de PubMed, de aquellos estudios que analizan la etiología de la PCB y el porcentaje de resistencia de las distintas especies bacterianas a diversos antibióticos. Se emplearon los términos de búsqueda "Chronic", "bacterial" y "prostatitis".

Criterios de inclusión y exclusión. Los criterios de inclusión fueron: (i) artículos publicados en inglés o castellano; y (ii) publicados con anterioridad al día 1 de julio de 2021. Los criterios de exclusión fueron: (i) relación PCB-cáncer de próstata; (ii) revisión global de las PCB sin atender al análisis etiológico o a la resistencia antibiótica; (iii) teorías etiopatogénicas de la PCB; y (iv) tratamientos no basados en la antibioterapia. Se revisó la bibliografía de estos para evitar pérdidas.

Extracción de datos y síntesis de la información. Se han obtenido los microorganismos detectados y su sensibilidad a los antibióticos, agrupándose en forma de tablas.

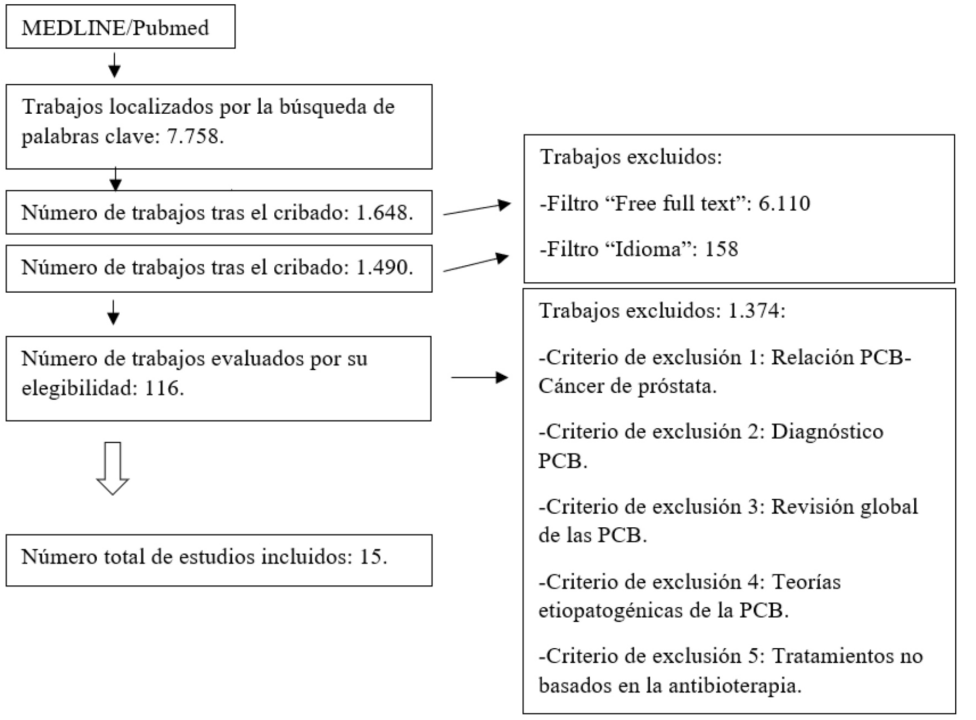

Figura 1 | **Diagrama de flujo de la revisión sistemática.**

Tabla 1 **Microorganismos causantes y su porcentaje de aislamiento en el estudio etiológico de prostatitis crónica bacteriana.**

Grupo bacteriano	Especie, n (%)	Aislados totales (n)	Prostatitis crónica bacteriana
Enterococcus spp.	*E. faecalis* 3.804 (87,50)	4.347	46,90% NIH-II clásicas
	E. faecium 297 (6,83)		44,10% NIH-II con bacterias atípicas
	Otros 246 (5,67)		
Staphylococcus spp.	Estafilococos coagulasa-negativos 1.626 (78,66)	2.067	22,30% NIH-II clásicas
	S. aureus 326 (15,77)		20,97% NIH-II con bacterias atípicas
	Otros 115 (5,57)		
Escherichia spp.	*E. coli* 1.399 (100)	1.399	15,09% NIH-II clásica
			14,20% NIH-II con bacterias atípicas
Bacterias atípicas	*Ureaplasma urealyticum* 251 (42,18)	595	
	Chlamydia trachomatis 211 (35,46)		
	Trichomonas vaginalis 100 (16,81)		
	Mycoplasma hominis 33 (5,55)		

RESULTADOS

Utilizando la metodología descrita, se obtuvieron 7.758 trabajos. Dicho número se redujo a 4.850 al aplicar el filtro "Full text"; y de ellos se recuperaron 1.648, que se redujeron a 1.490 una vez aplicado el filtro del idioma (español e inglés). Tras ser revisados todos ellos, y centrándonos en aquellos estudios en los que se investigaba microbiológicamente una muestra de sujetos con PCB, se eliminaron los que se focalizaban en el cáncer de próstata, los que ofrecían una revisión completa sin atender al análisis etiológico o a la resistencia antibiótica y aquellos relacionados con nuevas propuestas terapéuticas no basadas en antibioterapia, obteniendo 116 artículos. Finalmente, puesto que el objetivo de esta revisión es analizar la etiología de las PCB y el porcentaje de resistencia de las distintas especies bacterianas a diversos antibióticos útiles en esta entidad, se incluyeron 15 trabajos (Tabla 1- Material suplementario) que investigaban específicamente estos aspectos (Figura 1).

Estos estudios agrupan un total de 13.463 pacientes con prostatitis crónica o síndrome de prostatitis crónica (categorías II-III de la NIH). De todos ellos, 10.368 casos (77%) se incluyen en la categoría NIH-II clásica, es decir, se corresponden con la entidad denominada "Prostatitis crónica bacteriana" causada por bacterias de clara patogenicidad en esta entidad [6]. Si tenemos en cuenta la participación de bacterias atípicas (*Ureaplasma urealyticum, Mycoplasma hominis, Chlamydia trachomatis* y *Trichomonas vaginalis*) como agentes causales de PCB, el número de casos de prostatitis NIH-II asciende a 10.993 (81,65%). Por otro lado, 3.095 (23,00%) y 2.740 (18,35%), respectivamente, se corresponden con casos de prostatitis crónica NIH-III o síndrome de dolor pélvico crónico. Este análisis no ha tenido en cuenta el estudio de Wan CD et al [7], puesto que no ha sido posible obtener el número concreto de pacientes incluidos en la categoría NIH-II, proporcionando el estudio únicamente el número total de prostatitis crónicas.

La edad media de los pacientes en los distintos estudios es similar (30-50 años), excepto en el caso de Seo Y et al [8] (61,12 ± 12 años). En el estudio de Skerk V et al [9], el rango etario de los pacientes incluidos en el estudio oscila entre los 18 y 70 años, si bien el 74,8% de los pacientes tienen entre 20 y 50 años. El estudio de Stamatiou K et al [3] no describe la edad media de los pacientes incluidos en el estudio.

Para el diagnóstico, Cai T et al [10], Skerk V et al [9] y Stamatiou K et al [11] utilizaron el método de Meares-Stamey clásico [12]. Seo Y et al [8], Heras-Cañas V et al [13] y Heras-Cañas V et al [14] utilizaron una modificación del método clásico, que tiene una concordancia similar al método tradicional [15]. Mazzoli S [16] utiliza una nueva modificación de la prueba de Meares-Stamey, introducida por su grupo de trabajo, en la que incluyen un cultivo de semen adicional, complementando al resto de muestras del método clásico. Gracias a ello, se ha podido soslayar una de las grandes desventajas del método clásico: su fácil contaminación. Así, es posible descartar contaminaciones uretrales de la muestra, consiguiendo que los patógenos aislados en el cultivo sean verdaderamente representativos de su localización prostática. Stamatiou K et al [3] utiliza el método de Meares-Stamey clásico complementándolo en algunos casos con el cultivo del semen, con el objetivo de detectar casos de PCB en los que el método clásico es negativo.

El grupo bacteriano causal más frecuente es *Enterococcus* spp., aislándose en 4.347 casos, lo que corresponde con el 46,9% de los casos de prostatitis NIH-II clásica, y el 44,1% de las prostatitis NIH-II en las que se incluyen las bacterias atípicas. Dentro de este grupo, la especie más frecuentemente aislada fue *E. faecalis* (3804; 87,50%) y, en segundo lugar, *E.*

Tabla 2 **Resumen de la evolución en las resistencias antibióticas (%) según los datos analizados en esta revisión.**

Autores	Periodo de estudio	Microorganismo	Cantidad aislada	Trimetoprim-Sulfametoxazol	Ciprofloxacino	Levofloxacino	Norfloxacino	Tetraciclina	Macrólidos	Fosfomicina	Nitrofurantoína
Cai T e al (2011) [10]	1997-2008	*E. faecalis*	2745 (44%)	0,5%	3,3%	0,5%	11,5%	84,4%			0,25%
		E. faecium	101 (1,4%)	0,5%	31,25%	15%	34,25%	81,67%			0,5%
		S. aureus	280 (4,4%)	8,3%	29,25%	30%	34,25%	50%			11%
		S. haemolyticus	640 (10,2%)	8,5%	34%	35%	36,5%	42,7%			15,8%
		S. epidermidis	327 (5,2%)	25%	38,8%	27%	32%	48,4%			17,8%
		SCN	154 (2,4%)	25%	38,8%	27%	32,5%	48,4%			17,8%
		S. agalactiae	267 (4,2%)	16,8%	28,5%	16,5%	27,8%	26%			13,3%
		Otros estreptococos	87 (1,2%)	13%	22%	21%	28,3%	26%			29,5%
		Acinetobacter spp.	8 (0,1%)	16,3%	14,5%	10%	16,8%	35,4%			20%
		Citrobacter spp.	80 (1,2%)	9,5%	10,5%	7%	11,3%	35%			29,8%
		Enterobacter spp.	78 (1,2%)	1%	9,3%	3,5%	11%	40,7%			21%
		E. coli	698 (11,1%)	22,5%	9,3%	11,5%	18%	45%			17,8%
		K. oxytoca	144 (2,3%)	7,3%	8,3%	3,5%	8,5%	30,4%			21,5%
		K. pneumoniae	100 (1,5%)	9,3%	8,5%	3,5%	9,3%	33,4%			19%
		M. morganii	120 (1,7%)	8,8%	5%	3,5%	8,3%	30,7%			9,8%
		P. mirabilis	142 (2,2%)	10,5%	8,5%	2,5%	9,3%	33,4%			18,5%
		P. aeruginosa	44 (0,6%)		30,5%	10,5%	26,8%				
		P. putida	16 (0,1%)		29,8%	12%	26,8%				
		S. marcescens	190 (2,90%)		27,8%	19,5%	27,8%	33,4%			
Seo Y et al (2013) [8]	2007-2012	*E. faecalis*	41	31,5%	9,7%	4,8%	26,8%	97,5%			0%
Stamatiou K et al (2017) [11] *	2009-2015	*E. faecalis*	45			9,67%		29%	32,25%		
		E. coli	69	27,8%	16,7%	22,2%					
		P. mirabilis	12	26,1%	21,7%	21,7%					
		SCN	46	18%	5,6%	21,3%	24,7%				
		S. aureus	10								
Ibrahim N (2021) [22]	NC	*Staphylococcus* spp.	62 (60,8%)	20,6%	23,9%	20%		43,4%	57,8%	73,9%	0%
		Enterococcus spp.	14 (13,7%)	13,7%	6%	4,6%		16,9%	8,4%	15,9%	0%
		Streptococcus spp.	2 (2%)	5,9%	3%	6,2%		8,4%	8,4%	7,2%	7,4%
		Acinetobacter spp.	1 (1%)	0%	0%	0%					1,5%
		E. coli	14 (13,7%)	2,9%	4,5%	4,6%				1,4%	0%
		Proteus spp.	1 (1%)	1%	0%	0%					1,5%
		Morganella spp.	1 (1%)	1%	1,5%	0%					1,5%
		Klebsiella spp	2 (2%)	1%	0%	0%				1,4%	0%
Trinchieri A et al (2021) [18]	NC	*Enterococcus* spp.	22%	96%	21%	21%	77%	25%	19%		
		Staphylococcus spp.	13%	31%	21%	29%	42%	21%	21%		
		Streptococcus spp.	5%	9%	4%	50%	26%	0%	0%		
		Otros Gram +	2%	44%	40%	38%	20%	0%	17%		
		E. coli	31%	27%	20%	18%	20 %	11%	15%		
		Proteus spp.	4%	37%	12%	60%	0 %	22%	25%		
		Pseudomonas spp.	2%	100%	9%	100%	0 %	100%	100%		
		Klebsiella spp.	7%	41%	31%	43%	0 %	19%	50%		
		Otros Gram -	4%	23%	14%	67%	0 %	21%	29%		

***Datos correspondientes al grupo A del estudio. SCN: *Staphylococcus* coagulasa negativos.**

faecium (297; 6,83%); en un 5,67% de los casos no se especifica la especie responsable. El segundo género bacteriano más frecuentemente implicado es *Staphylococcus* spp, aislándose en 2.067 casos (22,30% de NIH-II clásicas y 20,97% de NIH-II con bacterias atípicas). El subgrupo más frecuentemente aislado son los estafilococos coagulasa-negativos (1626; 78,66%); a su vez, la especie más frecuente dentro de este subgrupo bacteriano fue *Staphylococcus haemolyticus* (756; 46,49%) y, en segundo lugar, *Staphylococcus epidermidis* (431; 26,50%); también se aisló 1 (0,0619%) *Staphylococcus hominis* y 1 (0,0619%) *Staphylococcus lugdunensis*. Además, dentro de este género encontramos 326 (15,77%) *Staphylococcus aureus*. En 115 casos no se especificó la especie (5,57%). En tercer lugar, se halla *E. coli*, aislándose en 1.399 ocasiones, lo que supone un 15,09% del total de casos de NIH-II clásica y un 14,20% de las NIH-II con bacterias atípicas. Por otra parte, cabe destacar el papel de las bacterias atípicas como agentes patogénicos de esta entidad en los trabajos revisados. Se han informado 595 (6,038%) episodios por microorganismos atípicas. Dentro de ellas, la más frecuente es *U. urealyticum* (251; 42,18%); a continuación, se encuentra *C. trachomatis* (211; 35,46%), *T. vaginalis* (100; 16,81%) y, finalmente, *M. hominis* (33; 5,55%) (Tabla 1).

Por último, el 98,64% (N: 9.721) de los aislados bacterianos se corresponden con cultivos monomicrobianos, mientras que sólo el 1,36% (N: 134) se corresponden con cultivos polimicrobianos. Dentro de ellos, el grupo más frecuentemente implicado es *Staphylococcus* spp., participando en 79 (59%) de los 134 cultivos polimicrobianos. En segundo lugar, se encuentra *E. coli* (53,7%) y, en tercer lugar, *E. faecalis* (50%).

Este análisis etiológico no ha tenido en cuenta los estudios de Choi Y et al [17], Wan CD et al [7] y Trinchieri A et al [18] ya que, la información relacionada con el número de microorganismos aislados solo se presenta en forma de porcentaje, sin especificar el número absoluto de bacterias que corresponde a cada valor porcentual.

El análisis correspondiente al porcentaje de resistencia de las especies bacterianas a diversos antibióticos útiles en esta entidad se resume en la Tabla 2.

DISCUSIÓN

Este estudio revela el viraje etiológico que está ocurriendo en las últimas décadas. Clásicamente se ha reconocido que las enterobacterias (fundamentalmente *E. coli*) son el principal género implicado en su etiología [11,14]. Actualmente, las bacterias grampositivas, fundamentalmente *E. faecalis*, se están erigiendo como los principales patógenos implicados en la PCB [10,19]. Y existe suficiente evidencia para afirmar que estos microorganismos, si se aíslan en una muestra adecuada de un paciente con síntomas prostáticos, son los causantes de dicha patología [10,19-21].

En diversos trabajos analizados en la revisión [10,16, 7] se observa la preponderancia de las bacterias grampositivas como los principales patógenos causantes de esta entidad; en el estudio de Mazzoli S et al [16], este grupo representó el 66% de los 1.686 aislados de pacientes con prostatitis crónica, incrementándose este porcentaje (73,9%) en el estudio de Cai T et al [10]. Por otra parte, en los estudios de Wan CD et al [7] y de Ibrahim N [22], *Staphylococcus* spp. fue el género más frecuentemente aislado, siendo *S. haemolyticus* la especie aislada en mayor proporción. Este es un hallazgo fundamental y que explicaría la razón de que las tasas de erradicación de *E. faecalis* sean inferiores a las de *E. coli* (50-70% vs 70-90%). Esto es así debido a que clásicamente, el tratamiento de primera línea de las PCB se basa en las fluoroquinolonas, antibióticos que tienen una mayor actividad frente a bacterias gramnegativas. De hecho, Bundrick W et al [19] mostró que, en la mayor parte de ocasiones, el tratamiento con fluoroquinolonas no superaba, o lo hacía levemente, la CMI de *E. faecalis* en fluido prostático.

Por otra parte, existen pocos estudios que analicen el uso de antibióticos que tengan una adecuada actividad frente a grampositivos, como linezolid o moxifloxacino. Wagenlehner FME et al [23] investigó el posible uso de moxifloxacino como agente terapéutico en esta entidad, encontrando una muy buena penetración prostática y una adecuada actividad tanto frente a bacterias grampositivas como gramnegativas.

Diversos autores [16,24] ya alertan acerca de la necesidad de modificar el protocolo terapéutico de la PCB; de lo contrario, si se continúan utilizando las fluoroquinolonas de forma empírica ante cualquier PCB (sin investigar su origen), es probable que se produzca un irremediable aumento de las resistencias antibióticas de este importante grupo antibiótico, además de que los pacientes afectados van a seguir siendo pacientes crónicos y con mínimas expectativas de mejora, teniendo en cuenta el impacto psicológico y el gasto sanitario que ello implica.

No obstante, también hemos de tener en cuenta el propio aumento de resistencias antibióticas que muestra *Enterococcus* spp. [25] dificultando aún más la elección antibiótica y la curación/remisión de estos pacientes. Sin embargo, una de las aportaciones fundamentales de este trabajo (que está además sustentada por una amplia evidencia reciente), es la consideración de las bacterias atípicas como agentes directamente implicados en la etiología de las PCB. Las guías de práctica clínica internacionales todavía no las reconocen como patógenas causales de esta entidad (NIH-II). Además, estudios pasados [26-28] ya hablaban del posible papel etiológico de las bacterias atípicas en la desconocida categoría NIH-IIIa. Skerk V et al [9] observó que, en una muestra de 1.442 pacientes con síntomas prostáticos crónicos, se aisló algún tipo de microorganismo en el 74% de los pacientes, encontrando con mayor frecuencia *T. vaginalis, C. trachomatis* y *Ureaplasma* spp.; los patógenos clásicos supusieron el 20% de los casos.

Otra bacteria atípica cuya implicación en la etiología de la PCB ha generado mucha controversia es *Chlamydia trachomatis* [29], ya reconocido como un microorganismo claramente causante de esta entidad [9, 30-32]. Además, sabemos que el curso sintomático de la PCB causada por este microorganis-

mo es más grave, con una tasa superior de recurrencias y con un mayor impacto en la calidad de vida, relacionándose con la eyaculación prematura y con una peor calidad de vida sexual [33]. Sin embargo, en la mayor parte de los estudios que investigan la etiología de la PCB se encuentra una pequeña cantidad de *C. trachomatis*. La explicación más plausible de este hecho es que, debido a que es una bacteria de crecimiento intracelular obligado, las muestras tradicionales que se utilizan para el diagnóstico de la PCB podrían no ser adecuadas, necesitando realizar técnicas moleculares (PCR) o pruebas más invasivas (Biopsia trans-rectal) para su adecuado aislamiento. Además, debido al desconocimiento general de esta entidad, un no desdeñable porcentaje de pacientes con síntomas prostáticos crónicos recibe ciclos de antibioterapia sin haber determinado la etiología infecciosa concreta, siendo posteriormente muy difícil aislar el verdadero microorganismo que estaba causando la enfermedad [34].

Por lo anterior, es crucial cambiar y estandarizar el concepto, procedimiento diagnóstico, clasificación y, por supuesto, el tratamiento que se utiliza rutinariamente, pues es ya evidente el más que demostrado papel causal que tienen las bacterias atípicas. La PCR es una técnica que notoriamente modifica el perfil etiológico que teníamos históricamente asumido; esta técnica, al no necesitar que los microorganismos sobrevivan en el laboratorio, permite identificar una mayor no se habían tenido en cuenta, como algunos grampositivos y, sobre todo, las bacterias atípicas [15]. Es necesario investigar y reclasificar [35] a muchos de los pacientes integrados en la categoría NIH-IIIa, pues muchos de ellos realmente sí tendrán un microorganismo que será la causa de sus síntomas [36].

En relación con la evolución de las resistencias antibióticas en los últimos años (Tabla 2), el estudio de Cai T et al [10] realiza un análisis entre los años 1997-2008. En este no se observaron diferencias significativas en el porcentaje de resistencia antibiótica de *E. faecalis* y *E. coli* a ciprofloxacino y levofloxacino. La tasa media de resistencia antibiótica de *E. faecalis* a este grupo antibiótico oscila en torno al 20% en casi todos los trabajos. Solo Cai et al [10] y Seo Y et al [8] han evidenciado diferencias: ciprofloxacino (3,3%) y levofloxacino (0,5%) en el primer caso, y ciprofloxacino (9,7%) y levofloxacino (4,8%) en el segundo; no obstante, ninguno ha analizado la evolución de la resistencia antibiótica en un periodo de tiempo.

Por otra parte, también es notable el incremento (23,03%) que se produce en la tasa de resistencia antibiótica de *E. faecalis* a las quinolonas en el primer grupo del estudio de Stamatiou K et al [11] (pacientes diagnosticados por primera vez de PCB), con respecto al segundo grupo, conformado por pacientes previamente diagnosticados y que tenían una recidiva de la enfermedad. Este hallazgo puede ser explicado por la teoría ampliamente aceptada de que la PCB es una patología cuyo origen, recidivas y falta de respuesta al tratamiento se debe a la existencia de biofilms bacterianos [37-42].

En la cohorte de 116 pacientes con PCB tratados durante 4 semanas con fluoroquinolonas en el estudio de Bartoletti R et al [39], un 85% de las bacterias aisladas eran productoras de biofilm. Ya Nickel JC et al [34] observaron que el 63% de las cepas de *E. coli* aisladas en su cohorte eran fuertes productores de biofilm, siendo este porcentaje ligeramente inferior (58%) en el caso de *E. faecalis;* en este estudio, la especie que con mayor frecuencia produjo biofilms fue *S. haemolyticus*. La presencia de biofilm incrustado en las calcificaciones prostáticas es el responsable del importante número de recidivas y de persistencia sintomática que padecen los pacientes con esta patología [43,44].

Por otra parte, también es reseñable constatar el alto porcentaje de resistencia antibiótica que *E. faecalis* muestra a eritromicina y tetraciclina. En el caso de tetraciclina, este hallazgo concuerda con la observado en otras publicaciones [2, 8]. En relación con eritromicina y el resto de los macrólidos, son fármacos que alcanzan una buena biodisponibilidad prostática gracias a sus características farmacocinéticas [45, 46]; además, tienen una muy buena actividad anti-biofilm [47], pudiendo ser potencialmente útiles en el tratamiento de las PCB causadas por microorganismos atípicos [48]. Estos hallazgos resaltan la importancia de realizar un diagnóstico etiológico y un perfil de resistencias previo a la indicación de cualquier terapia antibiótica en la PCB. De esta manera, eritromicina y el resto de los macrólidos son fármacos potencialmente útiles para el tratamiento de infecciones causadas por *Ureaplasma* spp., *C. trachomatis* o *M. hominis*.

En relación con *Staphylococcus* spp., debemos destacar el alto porcentaje de resistencia antibiótica que muestra hacia las quinolonas en diversos estudios, alcanzando cotas del 38,8% para ciprofloxacino y 27% para levofloxacino en el estudio de Cai T et al [10]. Sin embargo, Stamatiou K et al [11] encuentra tasas de resistencia del 5%. Sí es importante tener en cuenta el elevado porcentaje de resistencia antibiótica que muestra *Staphylococcus* spp. a fosfomicina (73,9%) en un estudio muy reciente [22], pero, en el resto de los estudios analizados en la revisión dicho porcentaje es bajo, siendo necesario realizar más estudios para valorar si dicho hallazgo está únicamente limitado a su zona geográfica (Iraq), o si es un fenómeno universal.

En relación con el análisis que nos ocupa, debemos discutir en último lugar el papel trimetoprim-sulfametoxazol. En la revisión observamos cómo, a excepción de Cai T et al [10], la tasa de resistencia antibiótica es elevada: 31,5% en el estudio de Seo Y et al [8] y 96% en el trabajo de Trinchieri et al [18]. En lo referente a *E. coli,* el porcentaje medio de resistencia en todos los estudios oscila en torno al 20-25%, encontrando Seo Y et al [8] una tasa de resistencia superior (31,5%).

Por último, el papel ampliamente demostrado de la implicación directa de bacterias grampositivas (distintas de *E. faecalis*) y de las bacterias atípicas en la etiología de las PCB, el reconocimiento del papel de los biofilms en las recidivas y la progresiva aparición de cepas bacterias resistentes a las fluoroquinolonas [49-53] nos plantea la necesidad de una modificación en el tratamiento de primera elección de esta entidad: fluoroquinolonas en monoterapia.

En conclusión, los microorganismos aislados más frecuentes en la revisión sistemática son *E. faecalis, Staphylococcus*

spp., *E. coli* y las bacterias atípicas, donde la resistencia antibiótica se encuentra en torno al 15-30% (con excepciones), lo que puede explicarse por la extensa utilización de antibióticos de forma empírica sin haber realizado un estudio de resistencias previo en la mayoría de los casos, resaltando la importancia de realizar un estudio microbiológico previo a la pauta de tratamiento antibiótico, disminuyendo así las recidivas y la cronicidad de esta entidad.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Brain abscesses caused by anaerobic microorganisms: a systematic review

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ABSTRACT

The objective of this study was to perform a systematic review of the characteristics, causative microorganisms and outcome of brain abscesses caused by anaerobic bacteria over the past 25 years. We reviewed studies on brain abscesses which included infection due to anaerobic microorganisms published between 1998 and 2022. We excluded reports with polymicrobial infections (more than 2 anaerobic bacteria isolated) and those that do not provide enough information to make comparisons, the reports with only one case of brain abscess due to anaerobes, as well as those focused on an only anaerobic bacterium. Also, we have excluded the cases in pediatric population. We searched the scientific literature through the Cochrane Library, EMBASE and PubMed/MEDLINE databases for studies of this condition. We finally included 28 studies with 6,167 patients, of which 715 (11.5%) were cases caused by anaerobic bacteria. There was a male predominance (70%) and mean age of 40.3 years. Most infections were monomicrobial (59.4%). The most common anaerobic microorganisms isolated were *Bacteroides* spp (43.4%) and Gram-positive anaerobic cocci (35.1%). Cases of brain abscesses caused by anaerobic bacteria were most frequent in Asia and Europe. The source of infection most frequent was otogenic in 84.6% followed by a neurosurgery procedure infection in 23% of patients. The main symptom observed was headache in 95.6% of patients followed by fever (69.5%). Surgical treatment was performed in 48 % of patients and the percentage of patients in whom antibiotic treatment was applied range 88.8% to 100%. The main limitation of this review is the non-inclusion of studies published before of 1998 in which MALDI-TOF MS system had not been introduced in the majority of laboratories for routine identification.

The patient rate with isolation of anaerobic bacteria in brain abscesses is low, but these data could be underestimated mainly due to the fastidious nature of these microorganisms and the difficulties in the identification of some anaerobes.

Keywords: Anaerobic bacteria; brain abscesses; *Bacteroides* spp; Gram-positive anaerobic cocci; neurosurgery; antibiotics

Abscesos cerebrales causados por microorganismos anaerobios: una revisión sistemática

RESUMEN

El objetivo de este estudio fue realizar una revisión sistemática de las características, los microorganismos causantes y evolución de los abscesos cerebrales causados por bacterias anaerobias en los últimos 25 años. Revisamos los estudios sobre abscesos cerebrales que incluyeron infección por microorganismos anaerobios publicados entre 1998 y 2022. Se excluyeron estudios con infecciones polimicrobianas (más de 2 bacterias anaerobias aisladas) y aquellos que no proporcionaban suficiente información para realizar comparaciones, los estudios con solo un caso de absceso por anaerobios así como aquellos focalizados solo en una bacteria anaerobia. También se excluyeron los casos en población pediátrica. Se realizó búsqueda de la literatura científica a través de la librería Cochrane y base de datos EMBASE y PubMed/MEDLINE para estudios con esas características. Se incluyeron finalmente 28 estudios con 6167 pacientes, de los cuales 715 (11,5%) fueron casos causados por bacterias anaerobias. Hubo predominio masculino (70%) y edad media de 40,3 años. La mayoría de las infecciones fueron monomicrobianas (59,4%). Los microorganismos anaerobios más comunes aislados fueron *Bacteroides* spp (43,4%) y cocos anaerobios grampositivos (35,1%). Los casos de abscesos cerebrales causados por bacterias anaerobias fueron más frecuentes en Asia y Europa. La fuente de infección más frecuente fue la otogénica en un 84,6% seguida de una infección por

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procedimiento de neurocirugía en un 23% de los pacientes. El principal síntoma observado fue la cefalea en el 95,6% de los pacientes seguido de fiebre (69,5%). Se realizó tratamiento quirúrgico en el 48 % de los pacientes y el porcentaje de pacientes en los que se aplicó tratamiento antibiótico oscila entre el 88,8 % y el 100 %. La principal limitación de esta revisión fue la no inclusión de estudios anteriores a 1998 en los que todavía no se había introducido MALDI-TOF MS en la mayoría de los laboratorios para el diagnóstico rutinario.

La tasa de pacientes con aislamiento de bacterias anaerobias en abscesos cerebrales es baja, pero estos datos podrían estar subestimados debido principalmente a la naturaleza fastidiosa de estos microorganismos y las dificultades en la identificación de algunos anaerobios.

Palabras clave: bacterias anaerobias; abscesos cerebrales; *Bacteroides* spp; cocos anaerobios grampositivos; neurocirugía; antibióticos

INTRODUCTION

Brain abscesses continue to remain a potentially fatal central nervous system infection [1]. This entity can be produced by several kinds of microorganisms such as bacteria, fungi, mycobacteria and parasites and the reported incidence ranges from 0.4 to 0.9 cases per 100,000 inhabitants [2,3]. This infection is usually described to be of polymicrobial nature involving both aerobic and anaerobic microorganisms [4]. The most important predisposing conditions resulting in the formation of brain abscesses are some underlying diseases (e.g. HIV infection), immunosuppressive treatments, disruption of the natural brain protective barriers or a systemic source of infection [5]. Brain abscesses caused by anaerobic bacteria can be mainly due to contiguous spread from parameningeal foci of infection as a consequence of paranasal, odontogenic and middle ear sources [6]. These microorganisms are not well routinely isolated in the majority of laboratories due to the difficulties in the isolation procedures. This circumstance has contributed to the fact that few studies are focused on brain abscesses caused only by anaerobic pathogens [4, 7-12]. Thus, the literature has provided only limited guidance with respect to the patients diagnosed with this condition, so the main objective of this study was to review the scientific literature containing cases of brain abscesses caused by anaerobic bacteria.

METHODS

Sources of information and selection of studies. Using the key words "brain abscesses", "brain abscess anaerobes" "cerebral abscesses" and "brain abscess anaerobic bacteria" we searched the medical literature through the Cochrane Library, EMBASE and PubMed/MEDLINE databases for studies of this condition. We also checked the references cited in the papers for additional reports searching patients with brain abscesses caused by anaerobes and that were described in sufficient detail to allow for comparison.

Inclusion and exclusion criteria. We have included studies with brain abscesses caused by anaerobic bacteria published in the scientific literature between 1998 and 2022, since during this period more and more laboratories use the MALDI-TOF MS or sequencing for identification of anaerobes isolated from serious infections. Our series included adult patients with brain abscesses in which anaerobic bacteria were isolated. Some reports have been excluded because they do not provide enough information to make comparisons, as well as the case reports with only one case of brain abscess due to anaerobes or those focused on an only anaerobic bacterium. Also, we have excluded the cases included exclusively in pediatric studies. We have excluded those in which more than three bacteria were isolated considering as mixed cultures [12].

Extracting of data and synthesis of information. Data were extracted reading these articles and recording them in a file. Later, these data were analyzed, synthetized and compared for establish conclusions.

RESULTS

A review of the literature identified 28 published large reports of brain abscesses whose etiology included anaerobic bacteria presenting data from 1998 to 2022 (Figure 1).

General characteristics. Clinical and microbiologic features of all patients included in this review are displayed in Table 1 and Table 2. Overall number of cases of brain abscesses included in this review was 6,167 and those with anaerobic microorganisms were 715 (11.5%) cases. The number of patients included per study varies between 4 and 2,219 patients, and the number of patients included per study with anaerobic bacteria varies between 2 and 190. There were 70% men (data not reported in 3 studies) and the mean age of patients was 40.3 years (data not reported in 5 studies). The cases were distributed as follows: 9 from India [4,8,9,11,13-17], 4 from Taiwan [18-21], 3 from Spain [12,22,23], 3 from France [7,24,25], 2 from UK [26,27], and one each from USA [28], Italy [29], Finland [30], Hungary [10], South Africa [31], Denmark [3] and Pakistan [32].

No underlying risk factors for anaerobic infection were reported in the majority of studies, although some factors such as immunosuppression, diabetes mellitus, surgery and cancer were observed in some works [3,12,23,24,26,31]. Regarding to the location of abscesses, it was not reported in three studies. From the remaining 25, the main location was the frontal lobe (84%), followed by temporal lobe (60%) and parietal lobe (40%).

Clinical features and source of infection. The most common predisposing conditions found were the presence of a contiguous focus of infection, especially an otogenic focus (84.6%). Other sources of infection also seen were the presence of a previous neurosurgery procedure (23%), a thoracogenic focus (16.9%), and a hematogenous focus (19.2%).

The clinical features in the patients included here were

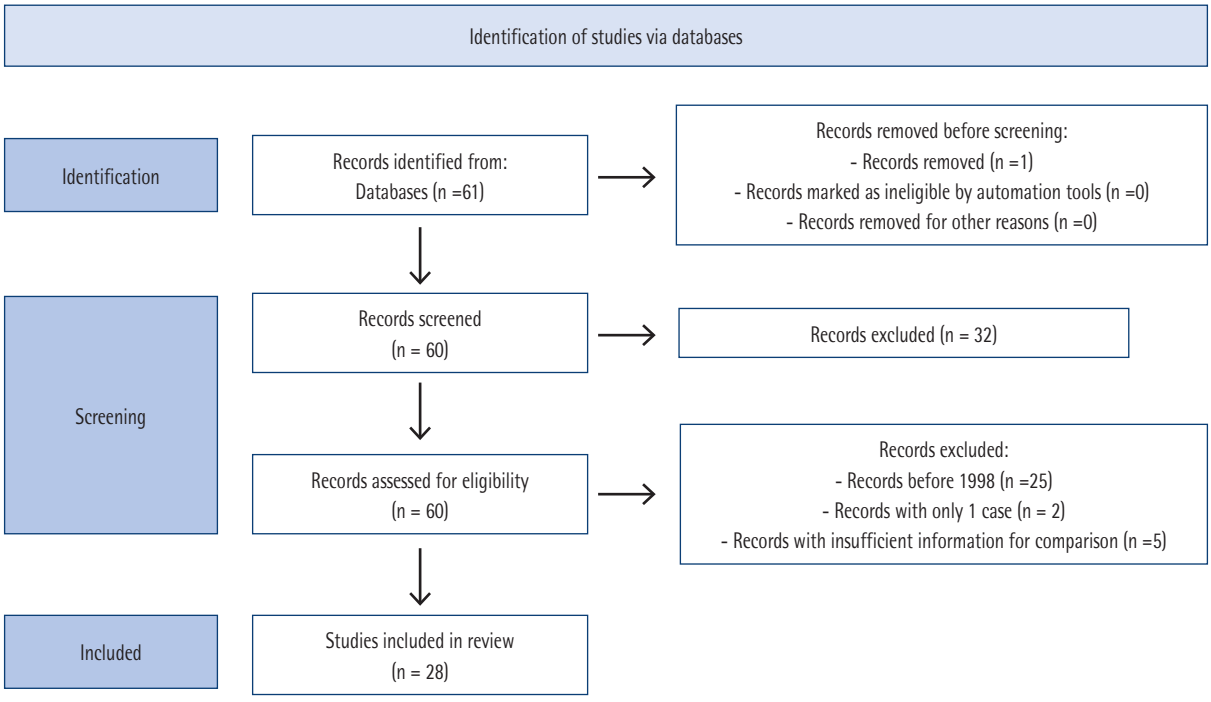

Figure 1 | **Flow diagram of cases of brain abscess included in this systematic review.**

calculated from 23 studies including 3,092 patients. The classic symptoms and signs were seen in many patients: headache was the most frequent and it was reported in 95.6% of cases, fever in 69.5% and neurologic deficit in 17.3%; vomiting only was detected in 8.6% of patients. Headache plus fever was detected in 65.2% of patients.

The relationship between the source of infection and the anaerobic microorganisms causing the brain abscesses was analyzed only in 3 studies [10,12,28]. They included only 74 patients. The most important finding in these cases is that the presence of a previous neurosurgery procedure was related with infection by *C. acnes* [10,12], and a relationship between the presence of sinuses infection and *Fusobacterium* spp was found [30].

Microbiology: type of infection and main anaerobic bacteria isolated. From 6,167 patients, at least one anaerobic bacteria was isolated in 715 (11.5%) of them. All cultures were performed from samples obtained by different surgical techniques such as aspiration/drainage and excision. Detailed microbiological methods related to the culture procedure and the identification of pathogens were only reported in 14 (50%) studies [4,7,8-15,18,21,22,28], and there were so many differences in the microbiological methodologies used. Overall results of the cultures yielded a total of 546 anaerobic bacteria isolated from the brain abscesses. The most frequently cultured microorganisms belonged to the *Bacteroides* genus (237 isolates, 43.4%), followed by Gram-positive anaerobic cocci (GPAC)/anaerobic *streptococci* (192 isolates, 35.1%). The third most common group of bacteria identified was *Fusobacterium* species (68 isolates, 12.4%). Table 3 shows all group of anaerobic bacteria isolated in the studies included in this review.

Regarding to the presence of monomicrobial or polymicrobial infection, this item was not reported in 12 studies; from the remaining 16 works, the infection was considered monomicrobial in 273 (59.4%) patients whereas it was considered polymicrobial in 186 (40.5%) cases.

Treatment and outcome. Initial antimicrobial therapy strategies were reported for 24 studies which included 3,362 patients. The percentage of patients in whom antibiotic treatment was applied range 89% to 100%. Treatment with antibiotics was very diverse, so no interesting conclusions could be drawn. On the other hand, data on surgical treatment were provided in 24 studies of those included here. Of them, 2,701 (43.7%) of patients were treated surgically by means of different techniques. Regarding to neurosurgical treatment modality, abscess aspiration and drainage was performed in 2,203 (81.5%) patients whereas primary abscess excision was done in 498 (18.4%) patients.

A total of 391 from 6,167 patients (6.3%) with brain abscesses died (ranging to 0% to 32%).

Table 1 Data of brain abscesses caused by anaerobic bacteria.

Author/year [reference]	Country	Total cases	Number of cases with anaerobes (%)	Men/women	Mean age (years)	Monomicrobial vs. polymicrobial (anaerobic brain abscesses)	Main anaerobic microorganisms isolated (n)	Main abscess's location	Source of infection
Chaudhry R/1998 [4]	India	18	6 (33.3)	14/4	23	2/4	*Prevotella* spp (4) *Bacteroides* spp (3)	Temporal and parietal	Thoracogenic and otogenic
Lu CH/2002 [18]	Taiwan	123	17 (13.8)	92/31	42	NR	*Bacteroides* spp (7) *Fusobacterium* spp (3)	Frontal and temporal	Hematogenous and neurosurgery
Kao PT/2003 [19]	Taiwan	53	5 (9.4)	34/19	41	2/3	*Bacteroides fragilis* (2) *Peptostreptococcus* spp (2)	Frontal and temporal	Otogenic and neurosurgery
Tattevin P/2003 [24]	France	94	15 (15.9)	74/20	47	NR	*Bacteroides* spp (5) *Anaerobic streptococci* (10)	NR	Dental abscess and thoracogenic
Le Moal G/2003 [7]	France	42	22 (52.3)	28/14	55	13/9	*Fusobacterium nucleatum* (14) *Prevotella* spp (8)	Temporal and frontal	Contiguous infection and trauma
Su TM/2003 [20]	Taiwan	124	18 (14.5)	93/31	40.7	NR	*Bacteroides* spp (7) *Fusobacerium* spp (3)	Frontal and temporal	Hematogenous and contiguous
Ni YH/2004 [21]	Taiwan	24	2 (8.3)	17/7	41	1/1	*Bacteroides fragilis* (1) *Peptostreptococcus* spp (1)	Frontal and parietal	Liver abscess and otogenic
Brook I/2005 [28]	USA	10	9 (90)	6/4	30	2/7	*Fusobacterium* spp (6) *Prevotella* spp (3)	Frontal	Contiguous infection
Prasad KN/2006 [13]	India	118	27 (22.8)	95/23	28	19/8	*Bacteroides fragilis group* (11) *Peptostreptococcus* spp (11)	Temporal, frontal and parietal	Otogenic
Tseng JH/2006 [26]	UK	142	24 (16.9)	98/44	41.5	NR	Anaerobes (24)	Frontal and temporal	Hematogenous and contiguous
Tonon E/2006 [29]	Italy	100	4 (4)	NR	49	4/0	*Peptostreptococcus* spp (2)	Frontal and parietal	Hematogenous and otogenic
Gómez J/2008 [22]	Spain	108	13 (12)	66/42	45	NR	*Bacteroides fragilis* (6) *Peptococcus* spp (5)	Temporal and frontal	Otogenic
Menon S/2008 [14]	India	75	16 (21.3)	55/20	NR	12/4	*Prevotella* spp (5) *Bacteroides* spp (9)	Temporal and frontal	Otogenic
Gutiérrez-Cuadra M/2009 [23]	Spain	71	5 (7)	52/19	45	5/0	*Peptostreptococcus* spp (2)	Frontal	Otogenic and neurosurgery
Lakshmi V/2011 [15]	India	352	39 (11)	2.7:1 ratio	28	22/17	*Peptostreptococcus* spp (17) *Bacteroides* spp (4)	Parietal and frontal	Otogenic
Nathoo N/2011 [31]	South Africa	973	37 (3.8)	722/251	24	NR	*Bacteroides* spp (31)	Frontal and parietal	Otogenic and traumatic
Manzar N/2011 [32]	Pakistan	53	8 (15.1)	41/12	NR	NR	Anaerobes (8)	Frontal and temporal	Sinus and neurosurgery
Mathis S/2012 [25]	France	81	25 (30.8)**	46/35	47	NR	*Fusobacterium* spp (NR) *Peptostreptococcus* spp (NR)	Frontal and parietal	NR
Helweg-Larsen J/2012 [3]	Denmark	102	14 (13.7)	66/36	47	NR	*Fusobacterium* spp (4)	Frontal and parietal	Contiguous and hematogenous
Das SK/2013 [16]	India	104	8 (7.6)	79/25	NR	6/2	*Bacteroides* spp (4)	Temporal and parietal	Otogenic
Vishwanath S/2016 [8]	India	4	4 (100)	2/2	32.5	1/3	*Bacteroides* spp (2) *Fusobacterium* spp (2)	Frontal	Otogenic
Sudhaharan S/2016 [9]	India	430	48 (11.1)	2.7:1 ratio	NR	31/17	*Peptostreptococcus* spp (30) *Bacteroides* spp (18)	Temporal	Otogenic

Table 1 Data of brain abscesses caused by anaerobic bacteria (cont.)

Author/year [reference]	Country	Total cases	Number of cases with anaerobes (%)	Men/women	Mean age (years)	Monomicrobial vs. polymicrobial (anaerobic brain abscesses)	Main anaerobic microorganisms isolated (n)	Main abscess's location	Source of infection
Laulajainen-Hongisto A/2016 [30]	Finland	166	45 (27.1)	117/49	42	NR	*Fusobacterium* spp (23)	Frontal and temporal	Contiguous
Singh N/2017 [17]	India	104	6 (5.7)	78/26	NR	NR	*Bacteroides* spp (6)	Temporal and cerebellar	Otogenic
Widdrington JD/2018 [27]	UK	113	43 (38)	73/40	53	11/32	*Fusobacterium* spp (10) *Prevotella* spp (7)	Frontal and temporal	Contiguous and neurosurgery
Gajdács M/2019 [10]	Hungary	64	34 (52.7)	32/32	52	NR	GPACs (16) *Cutibacterium acnes* (9)	NR	NR
Shruthi U/2019 [11]	India	2219	190 (8.5)	138/52*	22	127/63	*Bacteroides* spp (121) GPACs (97)	NR	Otogenic
Cobo F/2022 [12]	Spain	300	31 (10.3)	175/125	53	15/16	*Cutibacterium acnes* (13) *Parvimonas micra* (8)	Frontal and parietal	Neurosurgery and unknown

USA: United States of America; UK: United Kingdom; NR: not reported; GPAC: Gram-positive anaerobic cocci; * Referred to anaerobic microorganisms; ** Referred to overall patients.

DISCUSSION

Overall, data on brain abscesses caused specifically by anaerobic bacteria are currently limited. Searching the medical literature, only 7 studies described in detail the characteristics of brain abscesses caused by anaerobes [4, 7-12]. Taken into account the 28 studies focused on brain abscesses included in this review, the presence of anaerobes in these infections occurs in 11.5% on average (715 patients from 6,167). However, these data could be underestimated due to several facts such as the fastidious nature of these microorganisms, the special growth conditions required for the isolation of anaerobic pathogens and the difficulties in the identification. In the data reviewed here, it can see that this infection was more frequent in males (70%, n= 3,066 patients) and the mean age of the patients was 40.3 years. From 28 studies, in 21 (84%) the main location of these abscesses was the frontal region, followed by the temporal region (n= 15, 60%) and the parietal area (n= 10, 40%). The area less affected by brain abscesses was the occipital region. *Bacteroides* species were the most common anaerobic microorganisms isolated (237 strains), followed by GPACs (192 isolates). The majority of studies were published in Asia (n= 14), followed by Europe (n=12). There were no significant differences regarding the etiology according to the different regions. The relationship between the etiologic microorganism and the source of infection was only analyzed in 2 studies, including ours. In these published investigations a relationship between the presence of *Fusobacterium* spp and a sinusal focus seems that it could be demonstrated [28]. Also, our data showed a clear relationship between the presence of *Cutibacterium acnes* isolated in pure culture in patients with brain abscess that suffered a previous neurosurgery procedure [12]. Another study recently published also showed *C. acnes* as the second most frequent isolate in that series, although the authors cannot establish any relationship with a possible source of infection [10]. It is important to know the relationship between the source of infection and the causal microorganism in order to establish the empirical therapy of choice in these patients. However, further studies focused on this matter will be necessary to draw some conclusions. Taken together the data above mentioned, the empirical treatment should include effective drugs against *Bacteroides* spp and GPACs, taking into account the patterns of resistance in each area. In this sense, routine antimicrobial susceptibility testing for anaerobic bacteria could provide some interesting data and highlights the need to the resistance analysis for anaerobic isolates, especially in order to establish an adequate empirical therapy according to the local microbiological patterns and to modify the treatment when resistant strains appears.

The etiology of brain abscesses has been usually considered of polymicrobial nature, involving a great variety of aerobic and anaerobic microorganisms. However, from 715 anaerobic microorganisms corresponding to 28 studies, the majority of them were isolated as monomicrobial infections (n= 273, 59.4%) *vs* 186 isolates (40.5%) obtained as polymicrobial infections.

Regarding to the clinical features, none of the signs or symptoms presented in these patients are diagnostic of brain abscess. This symptomatology is only indicative because it can also be present in other diseases such as brain tumors and other central nervous system infections. In fact, in 5 studies the symptomatology was not reported; from the remaining 23

Table 2 **Data of brain abscesses caused by anaerobic bacteria related to clinical features, antimicrobial therapy, surgical treatment and mortality.**

Author/year [reference]	Main clinical features	Antimicrobial therapy n (%)	Surgical treatment n (%)	Overall mortality n (%)
Chaudhry R/1998 [4]	Headache, fever	NR	NR	1 (5.5)
Lu CH/2002 [18]	Headache, fever	123 (100)	106 (86); 72 excision; 40 aspiration and drainage	21 (17)
Kao PT/2003 [19]	Headache, fever	53 (100); 20 only antibiotics	33 (62.2); 25 aspiration and drainage; 8 excision	17 (32)
Tattevin P/2003 [24]	Headache, fever	88 (89)	60 (63.8); 47 aspiration and drainage; 7 excision	24 (26)
Le Moal G/2003 [7]	Headache, neurologic deficit	42 (100); 7 only antibiotics	42 (100)	6 (14)
Su TM/2003 [20]	Headache, fever	124 (100)	105 (84.6); 38 aspiration and drainage; 67 excision	21 (16.9)
Ni YH/2004 [21]	Headache, fever	24 (100)	20 (83.3); 19 excision	4 (16.6)
Brook I/2005 [28]	NR	10 (100)	10 (100)	NR
Prasad KN/2006 [13]	Headache, fever	118 (100)	118 (100); 84 aspiration and drainage; 34 excision	17 (14.4)
Tseng JH/2006 [26]	Headache, neurologic deficit	142 (100)	122 (85.9); 108 aspiration and drainage; 14 excision	24 (16.9)
Tonon E/2006 [29]	Fever, neurologic deficit	100 (100) 28 only antibiotics	72 (72); 64 aspiration and drainage; 8 excision	8 (8.3)
Gómez J/2008 [22]	Headache, fever	108 (100)	NR	17 (15.7)
Menon S/2008 [14]	Headache, fever	75 (100)	75 (100)	7 (9.5)
Gutiérrez-Cuadra M/2009 [23]	Headache, fever	71 (100)	26 (36.6); 19 excision; 7 aspiration and drainage	15 (21.4)
Lakshmi V/2011 [15]	NR	NR	NR	NR
Nathoo N/2011 [31]	Headache, fever	NR	954 (97.1); 927 aspiration and drainage; 18 excision	130 (13.4)
Manzar N/2011 [32]	Headache, fever	53 (100)	53 (100); 29 aspiration and drainage; 24 excision	6 (11.3)
Mathis S/2012 [25]	Headache, fever	24 (92.3)*	12 (46.1); 4 aspiration and drainage; 6 excision	5 (9)
Helweg-Larsen J/2012 [3]	Headache, fever	102 (100); 13 only antibiotics	91 (89); 61 aspiration and drainage; 18 excision	19 (19)
Das SK/2013 [16]	Headache, vomiting	104 (100)	99 (95.1); 78 excision; 21 aspiration and drainage	11 (10.5)
Vishwanath S/2016 [8]	Headache	4 (100)	2 (100); 2 aspiration and drainage	0
Sudhaharan S/2016 [9]	NR	430 (100)	430 (100); aspiration and drainage	1 (0.2)
Laulajainen-Hongisto A/2016 [30]	Headache, fever	164 (98.7)	164 (99); 117 aspiration and drainage; 54 excision	12 (7)
Singh N/2017 [17]	Headache, vomiting	104 (100)	99 (95.1); 78 excision; 12 aspiration and drainage	11 (10.5)
Widdrington JD/2018 [27]	Headache, neurologic deficit	113 (100)	103 (91); 95 aspiration and drainage; 8 excision	6 (5)
Gajdács M/2019 [10]	NR	NR	NR	NR
Shruthi U/2019 [11]	NR	190 (100)	190 (100); 88 aspiration and drainage	8 (4.2) **
Cobo F/ 2022 [12]	Headache	31 (100)**	31 (100)** ; 27 excision; 4 aspiration and drainage	0 **

*** Referred to patients with hereditary haemorrhagic telangiectasia; ** Referred only to anaerobes**

reports, headache was the main symptom present in these patients (95.6%), fever (41%) and fever (69.5%) and neurologic deficit (17.3%). Analyzing the association of these symptoms, headache plus fever was present in 65.2% of patients whereas headache plus focal neurologic deficit was present in only 13% of them. The classic triad of headache, focal neurologic deficits and fever was very unusual.

The outcome of patients with brain abscesses was reported in 391 patients and the average death rate was 6.8% ranging from 0% to 32%. With few exceptions, this mortality rate has clearly improved over the years. Several factors have influenced in this fact such as improvement in both diagnostic and neurosurgical techniques and antimicrobial treatments as well. The most frequent neurosurgical treatment modality was the aspiration of the abscess following the drainage in 40% of patients. The use of modern stereotactic neurosurgical techniques CT or MRI-guided permits both the sampling for diagnostic purposes and the decrease of the brain pressure with fewer complications than before. Also, the improvement in the antimicrobial treatment regimens has contributed to the decrease in mortality in these patients. Different treatment guidelines have been used along these years but, before the

Table 3 **Anaerobic microorganisms isolated from brain abscesses in 28 studies.**

Group of microorganisms	Number (%)
Bacteroides spp	237 (43.4)
GPACs/Anaerobic streptococci	192 (35.1)
Fusobacterium spp	68 (12.4)
Prevotella spp	27 (4.9)
Cutibacterium acnes	22 (4)

GPAC: Gram-positive anaerobic cocci

80's, antimicrobial anaerobicides were not normally included as empiric treatment of these infections; however, metronidazole along with third generation cephalosporins (cefotaxime/ceftriaxone) was considered to be the most frequent empiric treatment in brain abscesses, according to some studies [3, 8, 9, 11].

This study has some limitations: firstly, reporting of data was highly diverse among studies due to their heterogeneity which makes comparisons difficult of some items. Secondly, most data here included were referred to overall brain abscesses, unable to distinguish between abscesses caused by aerobic pathogens from those caused by anaerobic microorganisms. Third, in some studies it is difficult to exclude both the cases located in the extra-axial CNS (e.g. subdural empyema,..) and the cases produced in children.

In conclusion, *Bacteroides* species and GPACs seem to be the globally the most frequent anaerobic bacteria isolated in brain abscesses. Few data about the relationship between source of infection and etiological microorganisms were provided, but in some studies a relationship between *Fusobacterium* spp and sinusal source and *C. acnes* and neurosurgical procedure could be established. Unlike what was previously published, brain abscesses are most frequent of monomicrobial nature and they occurred most frequently in males. The new neurosurgical techniques along with a better empiric antimicrobial coverage have currently improved the global outcome of these patients.

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CONFLICT OF INTEREST

Author declares no conflict of interest.

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Validez y utilidad del RAE-CMBD en el estudio de los pacientes hospitalizados con gripe

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RESUMEN

Objetivos. Conocer el impacto hospitalario de la gripe requiere enriquecer los registros de vigilancia epidemiológicos con otras fuentes de información. El objetivo de este estudio fue determinar la validez del Registro de Actividad de Atención Especializada – Conjunto Mínimo Básico de Datos (RAE-CMBD) en el análisis de los resultados asistenciales de los pacientes hospitalizados con esta infección.

Métodos. Estudio observacional retrospectivo de los adultos ingresados con gripe en un hospital terciario durante las temporadas 2017/2018 y 2018/2019. Se calculó la concordancia del RAE-CMBD con el registro de vigilancia epidemiológica de gripe (estándar de referencia), así como los principales parámetros de validez interna y externa. Se utilizaron modelos de regresión logística para el ajuste por riesgo de la mortalidad intrahospitalaria y duración de la estancia.

Resultados. Se lograron 907 (97,74%) emparejamientos únicos, con una concordancia interobservadores elevada (ƙ=0,828). El RAE-CMBD mostró una sensibilidad del 79,87%, especificidad del 99,72%, valor predictivo positivo del 86,71% y negativo del 99,54%. La razón de mortalidad ajustada por riesgo de los pacientes con gripe fue menor que la de los pacientes sin gripe: 0,667 (0,53–0,82) vs. 1,008 (0,98–1,04) y la razón de duración de la estancia ajustada por riesgo, mayor: 1,15 (1,12–1,18) vs. 1,00 (0,996–1,001).

Conclusiones. El RAE-CMBD es una fuente de información válida para el estudio del impacto de la gripe en la atención hospitalaria. La menor mortalidad ajustada por riesgo de los pacientes ingresados con gripe respecto de los demás ingresados, parece apuntar a la efectividad de las principales medidas clínicas y organizativas adoptadas.

Palabras clave: Gripe, RAE-CMBD, sistemas de vigilancia, vacunación, control de la infección.

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Validity and usefulness of the RAE-CMBD studying patients hospitalised with influenza

ABSTRACT

Background. Understanding the hospital impact of influenza requires enriching epidemiological surveillance registries with other sources of information. The aim of this study was to determine the validity of the Hospital Care Activity Record - Minimum Basic Data Set (RAE-CMBD) in the analysis of the outcomes of patients hospitalised with this infection.

Methods. Observational and retrospective study of adults admitted with influenza in a tertiary hospital during the 2017/2018 and 2018/2019 seasons. We calculated the concordance of the RAE-CMBD with the influenza epidemiological surveillance registry (gold standard), as well as the main parameters of internal and external validity. Logistic regression models were used for risk adjustment of in-hospital mortality and length of stay.

Results. A total of 907 (97.74%) unique matches were achieved, with high inter-observer agreement (ƙ=0.828). The RAE-CMBD showed a 79.87% sensitivity, 99.72% specificity, 86.71% positive predictive value and 99.54% negative predictive value. The risk-adjusted mortality ratio of patients with influenza was lower than that of patients without influenza: 0.667 (0.53-0.82) vs. 1.008 (0.98-1.04) and the risk-adjusted length of stay ratio was higher: 1.15 (1.12-1.18) vs. 1.00 (0.996-1.001).

Conclusion. The RAE-CMBD is a valid source of information for the study of the impact of influenza on hospital care. The lower risk-adjusted mortality of patients admitted with influenza compared to other inpatients seems to point to the effectiveness of the main clinical and organisational measures adopted.

Keywords: Influenza, RAE-CMBD, surveillance systems, vaccination, infection control.

INTRODUCCIÓN

La infección por virus gripales constituye la enfermedad transmisible con mayor incidencia durante el otoño-invierno, ocasionando en todo el mundo entre 145.000 y 650.000 muertes cada año [1], 40.000 de las cuales se producen en Europa [2]. En España, la máxima incidencia semanal de gripe reportada por el Sistema centinela de Vigilancia oscila entre 200 y 350 casos por cada 100.000 habitantes, con importantes diferencias interanuales y una duración del periodo epidémico de alrededor de 9 semanas [3]. Conocemos su sintomatología, métodos diagnósticos, medidas preventivas, posibilidades terapéuticas, complicaciones más frecuentes, así como la gravedad de algunos cuadros [4]. Pero es escasa la información respecto a las características y resultados asistenciales de los pacientes hospitalizados con gripe cada temporada, asociando costes que alcanzan en Reino Unido los 100 millones de libras anuales [5].

Los registros hospitalarios asociados a sistemas de vigilancia epidemiológica, que tienen como objetivo la prevención y control de la enfermedad, identifican a todos los pacientes con diagnóstico clínico y/o microbiológico, aportando una visión fundamental en la distribución espacial y temporal de los pacientes hospitalizados [6]. No obstante, la información frecuentemente se limita a datos agregados y con periodicidad semanal, reservando la recogida detallada de variables pronósticas para los pacientes que cumplen criterios de gravedad[3]. Además, por definición, contemplan únicamente los casos de enfermedad, no permitiendo la comparación con pacientes hospitalizados por otras causas.

Surge por ello la necesidad de explorar otras bases de datos que, partiendo de la identificación de los casos garantizada por los registros de vigilancia epidemiológica, los complementen con información clínica relevante y faciliten la disponibilidad de un grupo control. Entre estas fuentes de información, por la facilidad de obtención, menores costes y uniformidad de los datos en grandes cohortes poblacionales [7], destaca en España el Conjunto Mínimo Básico de Datos (CMBD), denominado desde 2016 Registro de Actividad de Atención Sanitaria Especializada (RAE-CMBD) [8]. Se trata de una base de datos que integra información administrativa y clínica de los pacientes atendidos en distintas modalidades asistenciales de atención hospitalaria y cuya utilidad ya se ha demostrado en la investigación de resultados en salud de otras condiciones clínicas, como el síndrome coronario agudo [9], la gastroenteritis aguda por rotavirus [10], las anomalías congénitas [11] o diferentes neoplasias [12]. Los estudios sobre patologías respiratorias que han utilizado datos del RAE-CMBD se han incrementado notablemente en los últimos años [13]. En el caso de la gripe, ha permitido describir el impacto de las hospitalizaciones [14], así como relacionar las tasas de gripe estacional con la mortalidad hospitalaria por enfermedades cardiovasculares agudas [15], asumiendo la validez del RAE-CMBD en las estimaciones, pero sin haberla contrastado con otras fuentes de información de carácter clínico.

Considerando todo lo anterior, nos marcamos un doble objetivo. En primer lugar, determinar la validez del RAE-CMBD, respecto a un registro de vigilancia epidemiológica de gripe (RVEG) utilizado como estándar de referencia, en la caracterización de los casos hospitalizados con esta patología. Además, estudiar los principales resultados de la atención a pacientes hospitalizados con gripe (mortalidad intrahospitalaria y duración de la estancia), respecto al resto.

MATERIAL Y MÉTODOS

Diseño del estudio. Se realizó un estudio observacional retrospectivo de los pacientes ingresados con gripe en el Complejo Asistencial Universitario de Salamanca (CAUSA), durante las temporadas de gripe 2017/2018 y 2018/2019. El CAUSA es un hospital terciario con 914 camas instaladas, que presta asistencia a 332.234 habitantes, englobando 36 Zonas Básicas de Salud. Se estudiaron los casos correspondientes a las temporadas gripales 2017/2018 y 2018/2019, que abarcan, en ambos casos, desde la semana epidemiológica 40 (1 de octubre y 30 de septiembre, respectivamente) hasta la 20 del siguiente año (19 de mayo y 18 de mayo, respectivamente).

Fuentes de información. Se utilizaron las siguientes fuentes de información: 1. El RVEG del CAUSA, donde se incluyen todos los pacientes ingresados con prueba de detección genómica positiva para virus gripales, con clínica compatible y criterios de hospitalización, y que forma parte del sistema de vigilancia, prevención y control de enfermedades transmisibles [16]. La información clínica y administrativa del RVEG se actualizó diariamente hasta el momento del alta y fue el sistema de referencia para la adopción de medidas organizativas durante las temporadas estudiadas; y 2. el RAE-CMBD, cuya elaboración resulta de obligado cumplimiento para todos los hospitales del Sistema Nacional de Salud español que recoge datos demográficos y clínicos, codificados con la Clasificación Internacional de Enfermedades, 10ª Revisión (CIE-10) correspondientes a los diagnósticos y procedimientos de los pacientes ingresados.

Aunque el RVEG y el RAE-CMBD tienen propósitos, alcances y estructuras diferentes, ambos comparten determinados atributos que facilitan el emparejamiento de los episodios de hospitalización [17], que se realizó en este estudio mediante la combinación del número de historia clínica del paciente y la fecha de ingreso, que resultó ser única porque ningún paciente con gripe ingresó dos veces en el mismo día durante el periodo de estudio, identificando los episodios del RVEG con los episodios del RAE-CMBD con código CIE-10 J09*, J10* o J11* como diagnóstico principal o secundario.

Variables de estudio. Los episodios de hospitalización registrados en el RAE-CMBD se clasificaron en dos grupos según su identificación en el RVEG (episodios con gripe) o no (episodios sin gripe) y se excluyeron los episodios registrados en el RVEG que no se pudieron emparejar con el RAE-CMBD. Se consideraron variables de estudio la mortalidad intrahospitalaria, definida como los episodios con exitus como motivo de alta, y la duración de la estancia, medida en días y calculada

como la diferencia entre las fechas de alta e ingreso de cada episodio de hospitalización.

Análisis estadístico. Se utilizó el coeficiente kappa de Cohen para evaluar la concordancia del RAE-CMBD con el RVEG, considerado como estándar de referencia y, para medir la validez del RAE-CMBD, se calcularon la sensibilidad (S), la especificidad (E), los valores predictivos positivo (VPP) y negativo (VPN) y el índice de Youden. El grado de acuerdo se interpretó según la escala de Landis y Koch [18].

Se consideraron variables dependientes para el ajuste de riesgo la mortalidad intrahospitalaria y la duración de la estancia. En el primer caso, se utilizó regresión logística binaria considerando como variables independientes el sexo y la edad del paciente, si el ingreso fue urgente o programado, el peso relativo y el riesgo de mortalidad del episodio de hospitalización, según los *All Patient Refined Diagnosis Related Groups* v.35 (APR-DRG). En el segundo, se utilizó regresión de Poisson o binomial negativa, según necesidad, con las mismas variables independientes, excepto el riesgo de mortalidad, y, además, la categoría mayor diagnóstica y el nivel de severidad del episodio según APR-DRG. En ambos ajustes, se excluyeron los episodios del RAE-CMBD correspondientes a pacientes menores de 18 años (no contemplados en el RVEG) y a episodios clasificados en APR-DRGs no válidos.

Se examinó la bondad del ajuste de cada modelo estimado para seleccionar el más adecuado y se calcularon los *odds ratio* (OR) y las razones de tasas de incidencia (IRR), según necesidad, así como sus intervalos de confianza al 95%. En los modelos de regresión logística, la calibración se analizó gráficamente tras agrupar a los pacientes en deciles con respecto a las probabilidades predichas y tabular las probabilidades medias predichas frente las observadas, y la discriminación se evaluó mediante el área bajo la curva *receiver operating characteristic* (AUROC). En las regresiones de Poisson o binomial, la bondad del ajuste se evaluó mediante el Pseudo R^2 de *McFadden*.

Para comparar las diferencias de resultados entre el grupo de pacientes con gripe y el de pacientes sin gripe se calculó: 1. la razón de mortalidad ajustada por riesgo (RMAR) como el cociente entre la mortalidad observada y la esperada, obtenida a partir de las predicciones individuales del modelo de regresión logística y 2. La razón de duración de la estancia ajustada por riesgo (REAR) como el cociente entre la duración de la estancia observada y la esperada, obtenida a partir de las predicciones individuales de los modelos de regresión de Poisson o binomial negativa, según necesidad. En ambos casos, se utilizó la aproximación de *Byar* al test exacto de Poisson para obtener los intervalos de confianza al 95% [19].

Las variables cuantitativas se expresaron como medias y desviaciones estándar o medianas y rango intercuartílico, en el caso de que su distribución no fuera normal, y las cualitativas, como frecuencias y porcentajes. Las comparaciones de las variables cualitativas se realizaron mediante la prueba de la Chi-cuadrado o el test exacto de Fisher y las cuantitativas, mediante el Test de la T de *Student* o la U de *Mann-Whitney*, según necesidad. Todos los test realizados fueron bilaterales y se consideraron significativos p-valores<0,05. Los análisis se realizaron con el programa IBM SPSS Statistics versión 26 (IBM Corporation, Armonk, NY, USA.).

RESULTADOS

Concordancia y validez del RAE-CMBD. En los años contemplados en el estudio, el porcentaje de episodios de hospitalización codificados en el CAUSA fue del 92,47% (2017), 93,99% (2018) y 96,23% (2019). Se logró un emparejamiento cercano al 100% (97,74%) entre las dos fuentes de datos utilizadas, identificándose en el RAE-CMBD 907 de 928 episodios incluidos en el RVEG durante el periodo de estudio. No pudieron emparejarse con el RAE-CMBD 21 casos de gripe presentes en el RVEG, suponiendo el 2,26% del total. No se observaron diferencias estadísticamente significativas entre fuentes de información en la edad media de los pacientes: 76,62 (D.E. 16,33) en el RVEG vs. 75,99 (D.E. 16,55), p=0,420; la proporción de mujeres: 50,1% vs. 47,2%, p =0,227; la estancia media: 7,66 (D.E. 7,67) vs. 8,22 (D.E. 10,04), p=0,191; el peso medio de los APR-DRGs: 0,97 (D.E. 1,05) vs. 1,01 (D.E. 1,19), p=0,445; y la tasa bruta de mortalidad: 9,8% vs. 8,2%; p=0,245, aunque sí se encontraron en la proporción de casos con transmisión nosocomial del virus de la gripe: 12,4% vs. 4,7%; p<0,001.

La concordancia interobservadores para la identificación de los episodios con gripe fue elevada: κ = 0,828 (0,808 – 0,847) y el RAE-CMBD mostró una S del 79,87% (77,19% - 82,54%) y una E del 99,72% (99,66% - 99,77%), con VPP del 86,71% (84,34% - 89,09%), VPN del 99,54% (99,47% – 99,61%) y un índice de Youden de 0,80 (0,77 – 0,82).

Mortalidad intrahospitalaria y duración de la estancia. Entre el 1 de enero de 2017 y el 31 de diciembre de 2019, se registraron en el RAE-CMBD del CAUSA 96.184 altas, de las cuales se excluyeron 7.498 (7,8%) por tener menos de 18 años y 5.355 (5,6%) por quedar agrupadas en APR-DRGs no válidos, de forma que la población de estudio utilizada para los ajustes de riesgo comprendió 83.331 (86,6%) episodios. De ellos, 898 (1,08%) fueron episodios con gripe, con mayor edad media que los episodios libres de gripe: 76,48 (16,17) años vs. 66,01 (19,83), p<0,001; y similar proporción de mujeres: 49,56% vs. 49,03%, p=0,779. La Tabla 1 recoge el resto de características de ambos grupos relevantes para los ajustes de riesgo de la mortalidad intrahospitalaria y la duración de la estancia. Ambos modelos de ajuste de riesgo se muestran en las Tablas 2 y 3. El AUROC, utilizado para evaluar la calibración y discriminación del modelo de ajuste de la mortalidad intrahospitalaria, fue de 0,86 (Figura 1) y el ajuste de la duración de la estancia presentó un Pseudo R^2 = 0,22.

Después de los ajustes de riesgo, se observó que los pacientes con gripe presentaron una RMAR significativamente menor que los pacientes sin gripe: 0,667 (0,53 – 0,82) vs. 1,008 (0,98 – 1,04). No se encontraron diferencias estadísticamente significativas en las comparaciones realizadas en el grupo de pacientes con gripe, entre aquellos que ingresaron con gripe adquirida en la comunidad y los casos de transmisión nosoco-

Tabla 1 **Diferencias en el perfil de los pacientes hospitalizados con gripe y sin gripe.**

	Episodios con gripe		Episodios sin gripe		
	n	%	n	%	p
Ingreso urgente	879	97,88	61.391	74,47	< 0,001
Ingreso programado	19	2,12	21.042	25,53	< 0,001
CMD 1: Sistema nervioso	7	0,80	5.232	6,35	< 0,001
CMD 2: Enf. y trast. del ojo	1	0,11	181	0,22	0,740
CMD 3: Enf. y trast. del oído, nariz y boca	336	37,42	1.892	2,30	< 0,001
CMD 4: Enf. y trast. del aparato respiratorio	334	37,19	10.827	13,13	< 0,001
CMD 5: Enf. y trast. del aparato circulatorio	30	3,41	10.122	12,28	< 0,001
CMD 6: Enf. y trast. del aparato digestivo	39	4,24	9.742	11,82	< 0,001
CMD 7: Enf. y trast. del hígado, sistema biliar y páncreas	15	1,67	4.341	5,27	< 0,001
CMD 8: Sistema musculoesquelético y tejido conjuntivo	3	0,33	9.184	11,41	< 0,001
CMD 9: Enf. y trast. de la piel, tejido subcutáneo o mama	2	0,22	1.820	2,21	0,001
CMD 10: Enf. y trast. del sistema endoc. nutrición y metabolismo	9	1,00	2.326	2,82	0,002
CMD 11: Enf. y trast. del riñón y vías urinarias	10	1,11	5.700	6,92	< 0,001
CMD 12: Enf. y trast. del aparato reproductor masculino	0	0	950	1,15	0,002
CMD 13: Enf. y trast. del aparato reproductor femenino	0	0	1.436	1,74	0,001
CMD 14: Embarazo, parto y puerperio	11	1,22	6.302	7,65	< 0,001
CMD 16: Enf. y trast. de sangre, hematopoyéticos y sist. inmunológico	5	0,56	943	1,14	0,136
CMD 17: Trastornos mieloproliferat. neoplasias mal diferenciadas	9	1,00	1.839	2,23	< 0,018
CMD 18: Enfermedades infecciosas	66	7,35	2610	3,17	< 0,001
CMD 19: Trastornos mentales	5	0,58	1.262	1,53	0,025
CMD 20: Uso de drogas/alcohol y trast. mentales orgánicos inducidos	1	0,11	692	0,84	0,028
CMD 21: Lesiones y envenenamientos y efectos tóxicos de fármacos	2	0,22	853	1,04	0,025
CMD 22: Quemaduras	0	0	39	0,05	0,902
CMD 23: Otras causas de atención sanitaria	1	0,11	2.531	3,07	< 0,001
CMD 24: Infecciones VIH	0	0	146	0,18	0,389
CMD 25: Politraumatismos	0	0	145	0,18	0,382
Nivel de riesgo de mortalidad menor	152	16,94	45.130	54,75	< 0,001
Nivel de riesgo de mortalidad moderado	245	27,28	20.939	25,40	0,212
Nivel de riesgo de mortalidad mayor	373	41,53	12.622	15,31	< 0,001
Nivel de riesgo de mortalidad extremo	128	14,25	3.742	4,54	< 0,001
Nivel de severidad menor	90	10,01	34.647	42,03	< 0,001
Nivel de severidad moderado	276	33,74	29.408	35,67	0,703
Nivel de severidad mayor	462	51,45	15.808	19,18	< 0,001
Nivel de severidad extremo	70	7,80	2.570	3,12	< 0,001
Peso medio APR-DRG (DE)	0,98	1,04	1,12	1,09	<0,001

APR-DRG: All patients refined Diagnosis Related Groups. CMD: Categoría mayor diagnóstica.

Tabla 2 **Ajuste de riesgo de la mortalidad intrahospitalaria**

	OR	P	IC 95%	
Mujer	1,05	0,131	0,99	1,12
Peso relativo APR-DRG	1,10	< 0,001	1,09	1,13
Edad	1,02	< 0,001	1,02	1,03
Riesgo mortalidad (Menor)				
Moderado	6,22	< 0,001	5,35	7,23
Mayor	15,62	< 0,001	13,36	18,25
Extremo	47,16	< 0,001	39,85	55,828
Ingreso urgente				
Ingreso programado	0,60	< 0,001	0,53	0,69
Constante	0,0014	< 0,001	0,001	0,0018

OR: Odds ratio. IC 95%: Intervalo de confianza al 95%. APR- DRG: All patients refined-Diagnosis Related Groups.

mial: 0,961 (0,50 - 1,55) vs. 0,633 (0,49 – 0,79), los pacientes vacunados y sin vacunar: 0,763 (0,48 – 1,10) vs. 0,480 (0,24 – 0,79) y los casos que presentaron gripe como diagnóstico principal y aquellos que la presentaron como diagnóstico secundario: 0,697 (0,52 – 0,90) vs. 0,569 (0,38 – 0,79).

Así mismo, en relación con la duración de la estancia, se observó que los pacientes con gripe presentaron una REAR significativamente mayor que los pacientes sin gripe: 1,15 (1,12 – 1,18) vs. 1,00 (0,996 – 1,001). En el grupo de pacientes con gripe, también se observó una REAR menor en aquellos pacientes que ingresaron con gripe adquirida en la comunidad que los casos de transmisión nosocomial: 1 (0,98 – 1,03) vs. 1,93 (1,85 – 2,02), en los pacientes vacunados que los pacientes sin vacunar: 1,08 (1,04 – 1,11) vs. 1,23 (1,19 – 1,27) y en los casos que presentaron gripe como diagnóstico principal respecto a aquellos que la presentaron como diagnóstico secundario: 0,99 (0,94 – 1,04) vs. 1,36 (1,3 – 1,42).

DISCUSIÓN

El estudio planteó como objetivos determinar la validez del RAE-CMBD, respecto a un RVEG, en el análisis de las hospitalizaciones de adultos con gripe y estudiar las posibles diferencias en los principales resultados asistenciales, en términos de mortalidad intrahospitalaria y duración de la hospitalización, entre los pacientes ingresados con y sin gripe. Los resultados obtenidos muestran un emparejamiento casi perfecto entre las fuentes de información analizadas y valores elevados para el RAE-CMBD en los principales parámetros de validez interna y externa. Además, los pacientes hospitalizados con gripe presentaron una mortalidad intrahospitalaria inferior y una duración de estancia superior a los pacientes sin gripe, una vez realizados los ajustes de riesgo correspondientes.

El RAE-CMBD identificó la práctica totalidad de los episodios incluidos en el RVEG. El emparejamiento alcanzado en nuestro estudio (97,74%), fue muy superior al mostrado en la validación de esta base de datos en la investigación de resultados del síndrome coronario agudo [9], donde se logró un 60,85% de emparejamientos únicos con el registro DIOCLES. El RAE-CMBD aplicado al estudio de la gripe mostró valores inferiores de S y VPP, y superiores de E y VPN, respecto a su utilización en el ámbito cardiovascular. Los resultados obtenidos en la validación del RAE-CMBD como registro de identificación de episodios de gripe muestran un mejor rendimiento que las investigaciones sobre la validación de esta y otras bases de datos similares en cáncer [12,20,21], donde reportaron emparejamientos con los registros específicos de alrededor del 80% y valores de VPP de entre el 50% y 70%. En cuanto a la S del RAE-CMBD, cercana al 70%, osciló entre el 42% de la leucemia y el 96% del cáncer de vejiga. La elevada validez interna y externa de nuestra validación con el RVEG, se encuentra en estándares similares a los demostrados para el estudio del ictus (S = 96,1%, E = 87,5% y VPP = 82,5%) [22]. En nuestra experiencia con los datos del CAUSA, consideramos que la realización de pruebas de detección genómica para virus gripales a los pacientes con clínica compatible y criterios de hospitalización, a diferencia del diagnóstico clínico en registros de otras patologías, contribuyó a la alta calidad de la información en las diferentes fuentes, mejorando su emparejamiento. Todo ello apunta a considerar el RAE-CMBD una fuente de información precisa para la valoración del impacto de la gripe estacional y, de manera extendida, para la investigación epidemiológica de la patología respiratoria [13].

A pesar de las interesantes propiedades del RAE-CMBD en el estudio de la gripe, a las que debemos sumar su rapidez y bajo coste en comparación con la recogida y análisis de datos primarios [23], nunca podrá reemplazar a los sistemas y registros de vigilancia epidemiológica. En primer lugar, su carácter retrospectivo impide la adopción de medidas clínicas y organizativas inmediatas, como la localización de pacientes o el acceso y circulación de visitantes en las instalaciones [6]. Además, nuestros resultados ponen de manifiesto la dificultad de las bases de datos administrativas para detectar los casos de transmisión nosocomial del virus (12,4% de casos nosocomiales según el RVEG y 4,7% según el RAE-CMBD). Entre las causas de este infra-registro de casos nosocomiales, podría encontrarse la mayor dificultad del RAE-CMBD para establecer temporalidad (respecto a registros específicos de vigilancia en los que las fechas de diagnóstico y/o inicio de síntomas son fundamentales y se revisan de manera detenida), así como la posibilidad de que algunos casos nosocomiales no se hayan registrado al haber sido "eclipsados" por el diagnóstico principal al ingreso del paciente, considerado generalmente de mayor relevancia que la gripe.

Este modo de transmisión, especialmente relevante en personas con condiciones clínicas de riesgo y edad avanzada [24], requiere un diagnóstico rápido de los casos, con frecuencia asintomáticos [25], que facilite su identificación temprana y el establecimiento de las precauciones ampliadas de transmisión por gotas, incluyendo la ubicación del paciente en ha-

Tabla 3 Modelo de ajuste de riesgo de duración de la estancia.

	IRR	p	IC 95%	
Edad	1,001	< 0,001	1,000	1,002
Mujer	0,996	0,725	0,974	1,018
Ingreso programado	0,894	< 0,001	0,862	0,927
Peso relativo APR-DRG	1,151	< 0,001	1,137	1,165
CMD 1: Sistema nervioso				
CMD 2: Enf. y trast. del ojo	0,927	0,349	0,790	1,059
CMD 3: Enf. y trast. del oído, nariz y boca	0,653	< 0,001	0,585	0,729
CMD 4: Enf. y trast. del aparato respiratorio	0,853	0,001	0,775	0,938
CMD 5: Enf. y trast. del aparato circulatorio	0,810	< 0,001	0,739	0,888
CMD 6: Enf. y trast. del aparato digestivo	0,989	0,824	0,900	1,087
CMD 7: Enf. y trast. del hígado, sistema biliar y páncreas	1,116	0,027	1,012	1,229
CMD 8: Sistema musculoesquelético y tejido conjuntivo	1,086	0,072	0,993	1,188
CMD 9: Enf. y trast. de la piel, tejido subcutáneo o mama	0,778	< 0,001	0,698	0,868
CMD 10: Enf. y trast. del sistema endoc. nutrición y metabolismo	0,845	0,001	0,762	0,935
CMD 11: Enf. y trast. del riñón y vías urinarias	0,796	< 0,001	0,723	0,876
CMD 12: Enf. y trast. del aparato reproductor masculino	0,755	< 0,001	0,674	0,846
CMD 13: Enf. y trast. del aparato reproductor femenino	0,635	< 0,001	0,559	0,720
CMD 14: Embarazo, parto y puerperio	0.585	< 0,001	0,528	0,647
CMD 16: Enf. y trast. de sangre, hematopoyéticos y sist. inmunológico	1,106	0,114	0,976	1,173
CMD 17: Trastornos mieloproliferat. neoplasias mal diferenciadas	0,974	0,621	0,876	1,082
CMD 18: Enfermedades infecciosas	1,062	0,240	0,961	1,173
CMD 19: Trastornos mentales	5,427	< 0,001	4,713	6,248
CMD 20: Uso de drogas/alcohol y trast. mentales orgánicos inducidos	2,923	< 0,001	2,606	3,278
CMD 21: Lesiones y envenenamientos y efectos tóxicos de fármacos	1,066	0,347	0,933	1,217
CMD 22: Quemaduras	0,840	0,329	0,592	1,192
CMD 23: Otras causas de atención sanitaria	0,669	< 0,001	0,592	0,756
CMD 24: Infecciones VIH	1,150	0,466	0,789	1,767
CMD 25: Politraumatismos	1,287	0,001	1,107	1,497
Nivel de severidad (Menor)				
Moderado	1,435	< 0,001	1,393	1,478
Mayor	1,885	< 0,001	1,827	1,945
Extremo	1,955	< 0,001	1,832	2,087
Constante	4,127	< 0,001	3,705	4,596

IRR: Razón de tasas de incidencia. IC 95%: Intervalo de confianza al 95%. CDM: Categoría diagnóstica mayor. APR- DRG: All patients refined-Diagnosis Related Groups.

bitación individual (o aislamiento de cohortes cuando no sea posible), el uso de mascarilla quirúrgica por parte de los profesionales durante la asistencia y la limitación del movimiento del paciente fuera de la habitación a las situaciones estrictamente necesarias. Los casos relacionados con la asistencia sanitaria son, en su mayoría, evitables [26] y, en una enfermedad que implicó en las temporadas incluidas en nuestro estudio un coste aproximado por hospitalización de entre 2.924€ y 3.230€ [5] (superando los 4.000€ en pacientes mayores de 75 años), se traduce en un notable incremento de costes [27] que

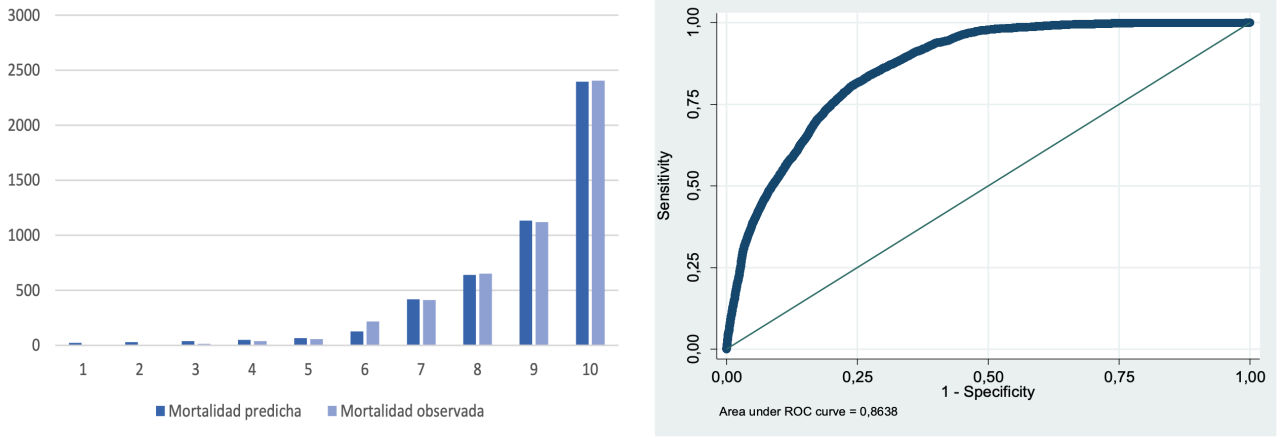

Figura 1 | **Calibración y discriminación del modelo de ajuste de la mortalidad intrahospitalaria.**

debe sumarse a las implicaciones clínicas y en seguridad del paciente.

Las propiedades del RAE-CMBD demostradas en esta investigación, si bien no permiten sustituir al RVEG, sí aportan información complementaria muy relevante sobre los resultados asistenciales de los adultos hospitalizados con gripe. Supone la continuación temporal del estudio que analizó los ingresos en el periodo 2009-2015 en España [14]. Además, actualiza el sistema de clasificación y codificación de enfermedades: CIE-9 en la investigación de San-Román-Montero et al. y CIE-10 [28] en nuestro estudio. El mencionado estudio, centrado en la determinación de las características que se asociaron con mayor mortalidad intrahospitalaria en la cohorte de ingresados con gripe (código diagnóstico utilizado, sexo masculino y determinados grupos de edad y condiciones clínicas de riesgo), obtuvo como principales conclusiones la necesidad de promover la vacunación antigripal anual, que en el modelo de duración de estancia ajustada a riesgo que presentamos disminuye la duración de la hospitalización, y la importancia de los sistemas de vigilancia epidemiológica, que hemos utilizado como *gold-standard* para la validación de la base de datos administrativa. En relación a la vacunación de pacientes y profesionales, con sólida evidencia reforzando su carácter protector de la aparición de la infección y sus complicaciones y mortalidad [29,30], el análisis del RVEG enriquecido con el RAE-CMBD añade a estos beneficios la disminución de la duración de la estancia en las personas con gripe vacunadas durante la temporada a estudio.

Consideramos que dos de los principales resultados obtenidos, la menor mortalidad y mayor duración de estancia ajustadas a riesgo de los pacientes hospitalizados con gripe respecto al resto de ingresados, pudieron ser consecuencia de la implementación de un exhaustivo sistema de vigilancia epidemiológica [16]. La coordinación de múltiples profesionales de diferentes servicios, con identificación inmediata y seguimiento estrecho de los casos y contactos pudo traducirse en mejores resultados en salud de los pacientes. El cumplimiento de estas medidas, que incluyen el aislamiento del paciente durante 7 días desde el inicio de los síntomas, siempre y cuando permanezca 24 horas sin fiebre o síntomas respiratorios [6] y, en algunos casos, la necesidad de disponer de una prueba de detección microbiológica negativa para su alta a otros centros sociosanitarios, pudieron dilatar la estancia.

Entre las principales limitaciones de nuestro estudio destacamos el análisis comparado del RAE-CMBD con el RVEG de un único centro. A pesar de que la información recogida en los sistemas de vigilancia epidemiológica debe responder a unos criterios mínimos comunes [3], cada centro puede enriquecerlos añadiendo variables de interés, afectando a la generalización de los resultados en lo relativo a la calidad del dato y el porcentaje de emparejamientos únicos. En segundo lugar, la investigación se limita al estudio de dos temporadas gripales. El RVEG del CAUSA mejoró notablemente en la temporada 2017/2018, impidiendo la comparabilidad con periodos previos, y las temporadas posteriores a las analizadas se encuentran claramente influidas por la pandemia causada por el SARS-CoV-2 [31]. Por último, tanto el RVEG como el RAE-CMBD recogen información del episodio de hospitalización del paciente. Por ello, y aunque constituya un elemento no diferencial entre bases de datos, eventos ocurridos tras el alta del paciente habrían pasado desapercibidos.

El elevado emparejamiento obtenido entre fuentes de información, superior al mostrado en las comparaciones con registros de otras patologías, y la discreta probabilidad de falsos positivos y falsos negativos, señalan al RAE-CMBD como una base de datos útil en el estudio del impacto de la gripe en la atención hospitalaria. La menor mortalidad ajustada a riesgo de los casos de gripe, respecto al resto de hospitalizados, parece apuntar a la efectividad de las principales medidas clínicas y organizativas adoptadas.

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CONFLICTO DE INTERESES

Los autores no presentan ningún conflicto de intereses

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Detección en urgencias de infección por VIH en pacientes que consultan por condiciones potencialmente relacionadas con infección oculta: Resultados iniciales del programa "Urgències VIHgila"

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RESUMEN

Objetivo. Estimar la prevalencia de infección por VIH desconocida en pacientes que consultan en servicios de urgencias hospitalarios (SUH) por las condiciones definidas en el Documento de Consenso (DC) de SEMES-GESIDA, evaluar la eficiencia de su implementación e investigar si en otras condiciones la determinación de serología VIH puede resultar eficiente.

Método. Se revisaron los resultados obtenidos en 10 SUH catalanes durante los 12 meses (julio-21 a junio-22) siguientes a implementar las recomendaciones del DC de solicitar serología VIH a pacientes con sospecha de infección de transmisión sexual, práctica de *chemsex*, solicitud profilaxis post-exposición (PPE), síndrome mononucleósico, neumonía comunitaria (18-65 años) o herpes zóster (18-65 años). Se consignaron también otros motivos de solicitud. Se calculó la prevalencia (%) de seropositividad global y para cada circunstancia, con su intervalo de confianza del 95% (IC95%). Se consideró la estrategia eficiente si el límite inferior del IC95% era >0,1%.

Resultados. Se realizaron 5.107 serologías VIH: 2.847 (56%) en situaciones especificadas en el DC, y 2.266 (44%) en otras 138 circunstancias. Se detectaron 48 infecciones por VIH desconocidas (prevalencia=0,94%; IC95%=0,69-1,24). La prevalencia fue algo superior en las solicitudes ajustadas al DC (30 casos, 1,12%) que en las que no (18 casos, 0,71%; p=0,16). La prevalencia individualizada para los motivos especificados en el DC osciló entre 7,41% (IC95%=0,91-24,3) en práctica de *chemsex* y 0,42% (IC95%=0,14-0,98) en PPE, y siempre resultó eficiente, con excepción de herpes zóster (0,76%, IC95%=0,02-4,18). Respecto al resto de motivos de solicitud, se detectaron casos en 12 circunstancias, y en cuatro la determinación podría ser eficiente: linfopenia (10%, IC95%=0,25-44,5), fiebre con poliartralgias-poliartritis (7,41%, IC95%=0,91-24,3), alteración conductual-confusión-encefalopatía (3,45%, IC95%=0,42-11,9) y fiebre de origen desconocido (2,50%, IC95%=0,82-5,74).

Conclusión. La determinación de serología VIH en los SUH en los procesos previamente definidos en el DC SEMES-GESIDA es eficiente. Se identifican algunas circunstancias adicionales que podrían ser añadidas a las previamente contempladas para aumentar la rentabilidad de esta estrategia.

Palabras clave: Urgencias, VIH, eficiencia, seroprevalencia.

Emergency detection of HIV infection in patients consulting for conditions potentially related to occult infection: Initial results of the "Urgències VIHgila" program

ABSTRACT

Objective. To estimate the prevalence of unknown HIV infection in patients who consulted in hospital emergency services (ED) for conditions defined in the SEMES-GESIDA Consensus Document (DC), evaluate the efficiency of its implementation and investigate the efficiency of HIV serology determination in other conditions.

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Methods. Results were reviewed in 10 Catalan EDs for 12 months (July-21-June-22) after implementing CD recommendations: request HIV serology in case of suspected sexually transmitted infection, chemsex, post-exposure prophylaxis (PEP), mononucleosis syndrome, community pneumonia (18-65 y-o) or herpes zoster (18-65 y-o). Other reasons for request were included. Prevalence (%) of global seropositivity and for each circumstance was calculated, with a 95% confidence interval (95%CI). The efficient strategy was considered if the lower limit of the CI95%>0.1%.

Results. A total of 5,107 HIV serologies were performed: 2,847(56%) in situations specified in CD, and 2,266 (44%) in other 138 circumstances. Forty-eight unknown HIV infections were detected (prevalence=0.94%;95%CI=0.69-1.24). The prevalence was somewhat higher in DC requests (30 cases 1.12%) than the rest (18 cases 0.71%; p=0.16). The individualized prevalence of CD reasons ranged between 7.41% (95%CI=0.91-24.3) in chemsex and 0.42% (95%CI=0.14-0.98) in PPE, always efficient except herpes zoster (0.76%; CI95%=0.02-4.18). In other reasons, cases were detected in 12 circumstances, and in four the determination could be efficient: lymphopenia (10%;CI95%=0.25-44.5), fever with polyarthralgia-polyarthritis (7.41%;CI95% =0.91-24.3), behavioral alteration-confusion-encephalopathy (3.45%;95%CI=0.42-11.9) and fever of unknown origin (2.50%;95%CI=0.82-5.74).

Conclusion. The determination of HIV serology in HES in the processes defined by DC SEMES-GESIDA is efficient. Some circumstances are identified that could be added to those previously contemplated to increase efficiency.

Keywords: Emergency, HIV, efficiency; seroprevalence

INTRODUCCIÓN

La infección por el virus de la inmunodeficiencia humana (VIH) continúa siendo un problema de salud mundial y en España existen unas 150.000 personas afectadas [1]. Una de las razones principales que impide el control sanitario de esta pandemia es que existe una proporción elevada de casos en los que dicha infección aún no es conocida por el paciente. Globalmente, se estima que el 20% de pacientes contagiados por VIH en el mundo no conoce su situación de seropositivo. En España, este porcentaje es inferior, alrededor del 13% [1,2], si bien difiere en función de cada comunidad autónoma. En el caso de Cataluña, se considera que el porcentaje es del 9% [3]. Muchos de estos casos se van a diagnosticar tardíamente, cuando la cifra de linfocitos CD4 es inferior a 350 por mm^3 [4,5]. El diagnóstico tardío del paciente conlleva a un peor pronóstico, un incremento del gasto sanitario y una perpetuación de la transmisión de la infección en la población [6]. Por todo ello, cualquier acción encaminada a incrementar el diagnóstico de infección por VIH debe considerarse de elevado interés sanitario desde la perspectiva de salud pública.

Desde esta óptica, muchos autores han destacado la oportunidad que supone poner en marcha mecanismos de detección de infección por VIH en los pacientes que consultan en los servicios de urgencias hospitalarios (SUH) [7-12]. Entre otras razones, el acceso al SUH es universal en la gran mayoría de países y, en muchos de ellos, supone además la única forma de acceso a la atención sanitaria de colectivos vulnerables entre los cuales la prevalencia de infección por VIH puede estar incrementada respecto a la población general. Las estrategias para llevar a cabo han sido diversas, desde una detección dirigida a determinados procesos en los que la prevalencia de infección se ha considerado más alta que en la población general hasta una determinación universal a todo paciente que consulte en los SUH, la cual un reciente análisis ha mostrado que podría resultar coste-eficiente [13]. De hecho, se acepta que, si la prevalencia en el ámbito en el que se practica el cribado es superior al 0,1%, dicha estrategia cabe considerarla coste-eficiente [14].

En línea con la estrategia de detección dirigida a ciertos procesos, el Grupo de Infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias (INFURG-SEMES) y el Grupo de Estudio del Sida (GESIDA) publicaron en 2020 un Documento de Consenso (DC) en el que se definía como buena práctica clínica el cribado dirigido de VIH en los SUH en 6 circunstancias clínicas que presentan una elevada prevalencia de infección por el VIH y que son motivos de consulta frecuentes en los SUH [15]. En todas ellas, lo esperable sería encontrar una prevalencia superior al 0,1%, que es la que determina su eficiencia [14,16]. Sin embargo, esta recomendación se basa en una opinión de expertos que no ha sido nunca testada en la práctica clínica real de los SUH. El programa "Urgències VIHgila" es un programa piloto cuya finalidad es la de implementar las recomendaciones del DC anteriormente comentado [15] en los SUH de Cataluña, y documentar la eficiencia que tiene la solicitud de una serología VIH en dichas situaciones. Además, pretende detectar otras situaciones, no contempladas en el documento original, en las que la solicitud de dicha serología VIH pudiera resultar también eficiente. El programa integró inicialmente a 10 SUH catalanes, y el presente trabajo presenta los resultados obtenidos tras los 12 meses iniciales. El objetivo principal es conocer la prevalencia de seropositividad en las 6 condiciones definidas en el DC, evaluar su eficiencia e investigar en qué otras circunstancias la determinación de una serología VIH en los SUH podría resultar eficiente.

MÉTODO

Diseño del estudio. El proyecto "Urgències VIHgila" fue puesto en marcha por la *Societat Catalana de Medicina d'Urgències i Emergències* (SoCMUE) en 2021 con el objetivo fundamental de implementar en 10 SUH de Cataluña las recomendaciones de solicitud de serología VIH en los pacientes que cumpliesen las 6 condiciones definidas por el DC SEMES-GESIDA [15]. Estas 6 condiciones son: pacientes que consultan por sospecha de infección de transmisión sexual (ITS), por problemas relacionados con la práctica de *chemsex*, que solicitan profilaxis post-exposición (PPE), en aquellos que se detecta un síndrome mononucleósico y en los pacientes de edad comprendida entre los 18 y 65 años en quienes se diagnóstica neu-

monía comunitaria o herpes zóster. La solicitud de serología era informada al paciente, quien debía consentir a ella. Dicho consentimiento verbal se recogía en la historia clínica.

La estrategia seguida para el reclutamiento de centros fue contactar desde la SoCMUE con los SUH que estuviesen interesados en implementar esta estrategia y ofrecer a 10 de ellos participar en un plan de implementación específico. La selección final de los 10 centros se hizo por conveniencia y con la intención de tener una representación balanceada de todo el territorio catalán, de manera que se incluyeron 5 SUH de la ciudad de Barcelona o municipios limítrofes (Hospital Clínic, Hospital de Sant Pau y Hospital del Mar en Barcelona y Hospital Universitari de Bellvitge en L'Hospitalet de Llobregat y Hospital Fundació Esperit Sant en Santa Coloma de Gramenet) y 5 correspondientes al resto de Cataluña (Hospital Parc Taulí de Sabadell, Hospital Althaia de Manresa, Hospital Doctor Trueta de Girona, Hospital Arnau de Vilanova en Lleida y Hospital Sant Pau i Santa Tecla en Tarragona). La SoCMUE nombró un grupo coordinador formado por dos médicos (OM y EG) y dos enfermeros (AV y EM) para llevar a cabo la implementación completa del proyecto.

El plan de implementación del DC tuvo diversas fases. En la primera, se seleccionó un médico coordinador en cada SUH (denominado *Champion*) que era el responsable último del desarrollo del programa en su centro. La segunda fase consistió en una reunión de los coordinadores del proyecto con todos los *Champions* para presentarles el programa y ofrecerles las pautas para que pusiesen a punto en cada centro el cronograma de trabajo para hacer posible la determinación de una serología VIH en urgencias, tal como indica el DC. Se hizo hincapié en que era fundamental tener bien organizados los circuitos con microbiología (para la recepción de las muestras y el retorno de los resultados) y con el servicio de infecciones o medicina interna (para poder referir a los pacientes detectados a sus consultas para completar el estudio e iniciar el tratamiento), así como en tener una estrategia de comunicación de los casos seropositvos a los pacientes, con una trazabilidad clara y con constancia documental de dicho contacto en la historia clínica del paciente. Cuando esa fase quedaba completada, se pasaba a la tercera fase que consistía en la una reunión *in situ* individualizada en cada SUH en la que los coordinadores del proyecto y el *Champion* local presentaban los detalles del proyecto y su implementación en el centro a todos los médicos y enfermeros de urgencias, así como a aquellos profesionales de otras especialidades involucrados en el proyecto. Además, se elegía un coordinador de enfermería de urgencias para que hiciese difusión entre todo el estamento y para que colaborasen de forma activa en el proyecto. En dicha reunión, se suministraba material recordatorio diverso (posters, pegatinas, calendarios de mesa, bolígrafos) y se hacía énfasis en la necesidad que estuviesen bien visibles en todo el SUH y sobre todo en los puntos en los cuales los profesionales pudiesen solicitar serologías. A partir de dicho momento, se consideraba que el centro había iniciado el programa. La cuarta fase consistía en el informe semanal de las serologías solicitadas, los motivos de la solicitud y su resultado. Ello lo lleva a cabo una profesional externa al proyecto, que actúa como *data manager* y dinamizadora social. Para ello se creó una página web específica (www.urgencies-vihgila.cat) donde los resultados se actualizan semanalmente, y que además contiene información divulgativa del proyecto. El proyecto "Urgències VIH-gila" cuenta también con cuentas específicas de Twitter y Facebook. La última fase consistía en reuniones presenciales periódicas cada 4 meses de los coordinadores del proyecto, los *Champions* y los coordinadores de enfermería de todos los SUH participantes para poner en común aspectos relativos a la marcha del proyecto. La finalidad es desarrollar o copiar estrategias que hubiesen resultado de éxito en algunos centros y evitar acciones con escasa repercusión en el objetivo de solicitar serologías VIH en las condiciones definidas por el DC.

Periodo de estudio. Todos los SUH se iniciaron entre los meses de mayo y junio de 2021, y el presente trabajo incluye los datos comprendidos entre el 1 de julio de 2021 y el 30 de junio de 2022 (12 meses).

Variables recogidas y análisis. Se recoge el número semanal y total de serologías realizadas en cada SUH, la razón de la solicitud y su resultado. En el caso que la solicitud no se ajustase a las circunstancias recogidas en el DC, se solicitó el motivo principal de realizar dicha solicitud. Se consideró que una serología positiva cumplía la condición de detección de nuevo caso cuando no había existido nunca previamente una serología positiva o bien cuando, a pesar de haber existir diagnóstico previo, el paciente no había realizado ningún tipo de control ni tratamiento en los 3 años previos. Estos se consideraron pacientes no controlados y fueron incluidos como nuevos casos para los propósitos del presente estudio. En todos los casos detectados, se anotó la cifra de linfocitos totales y CD4 en el momento del diagnóstico. Por otra parte, se consignó el número de casos en los que el contacto y citación para seguimiento fue posible, así como cuántos pacientes acudieron de forma efectiva a control tras el diagnóstico de VIH en el SUH.

Los resultados se expresan en promedios, y en números absolutos y relativos. La prevalencia de seropositivos se obtuvo dividiendo los casos positivos por el número de determinaciones realizadas, y se expresó en porcentajes, tanto para el global de solicitudes y centros, como para cada motivo de solicitud y para cada centro. Para las comparaciones de seroprevalencias, se utilizó el test de ji cuadrado. En el caso de determinaciones por circunstancias diferentes a las definidas en el DC, se analizaron los motivos y, para cada uno de ellos, se calculó también la prevalencia de seropositivos.

Dado que se acepta que la determinación de serología VIH es eficiente cuando la prevalencia es superior al 0,1% [14,16], se calculó el intervalo de confianza del 95% (IC 95%) de las proporciones de seropositivos, globales y para cada situación particular, y se consideró que las determinaciones habían sido eficientes si el límite inferior del IC 95% era superior a 0,1%.

Aspectos éticos. Dado que se trata del análisis de resultados de un programa formativo encaminado a mejorar la calidad asistencial prestada en los SUH que evalúa datos de carácter epidemiológico sin identificación de pacientes, no se

solicitó aprobación por parte del Comité de Ética. Todos los pacientes dieron su consentimiento para la determinación de la serología VIH como parte de la práctica asistencial recomendada por el DC.

RESULTADOS

Entre julio de 2021 y junio de 2022 (12 meses), se realizaron 5.107 serologías VIH en los 10 SUH participantes, lo cual supuso un promedio semanal de 98 determinaciones serológicas. Se observó un ritmo progresivamente creciente durante las primeras 8 semanas tras la implementación, pasadas las cuales el número de serologías solicitadas se estabilizó (Figura 1). De estas, 2.847 (56%) correspondieron a pacientes que se encontraban en alguna de las 6 situaciones especificadas en el DC, mientras que las 2.266 serologías restantes correspondieron a otras situaciones clínicas. Se observó que, durante la primera mitad del año, las determinaciones realizadas en el primer supuesto fueron siempre superiores a las del segundo supuesto, en tanto que en la segunda mitad del año el número de solicitudes en ambos supuestos se ha mostrado más parejo (Figura 1).

El detalle de solicitudes realizadas por centro y en función de la circunstancia que determinó su solicitud se recoge en la Tabla 1. El número de determinaciones osciló entre las 1.601 realizadas en el Hospital Clínic (promedio semanal: 31) y las 157 del Hospital Arnau de Vilanova (promedio semanal: 3). Por otro lado, el número de serologías realizadas en relación a las circunstancias detalladas en el DC osciló entre las 1.183 hechas a pacientes que solicitaron PPE (promedio semanal: 23) y las 27 realizadas a pacientes con práctica de *chemsex* (promedio semanal: 1). Hubo 2.266 solicitudes generadas por 138 circunstancias distintas a las definidas en el DC, entre las que destacan el estudio posexposición laboral, la fiebre de origen desconocido, la necesidad de diálisis urgente, las hepatitis y la neumonía por COVID-19, con más de 100 solicitudes cada una de ellas (Tabla 2).

En total, se detectaron 48 pacientes con infección por VIH, y la Tabla 3 resume los motivos de solicitud de serología VIH en urgencias en estos casos en los que el resultado fue positivo. De ellos, el 83% fueron diagnósticos *de novo* y el 17% restante correspondieron a pacientes no controlados desde hacía más de 3 años y que durante el proceso asistencial urgente no manifestaron su condición de seropositivos. El porcentaje de positividad global fue del 0,94% (IC 95%: 0,69-1,24) (Figura 2). Todos los pacientes ingresaron o fueron contactados de forma efectiva, si bien 7 de ellos no han acudido a la consulta de seguimiento (6 correspondían a diagnósticos *de novo* y 1 correspondía a un diagnóstico ya conocido tiempo atrás pero no controlado). Los linfocitos totales en el momento del diagnóstico en el SUH estaban por debajo de 1000/mm^3 en el 41% de casos, y los linfocitos CD4 determinados en la primera visita de control estaban por debajo de 350/mm^3 en el 61%.

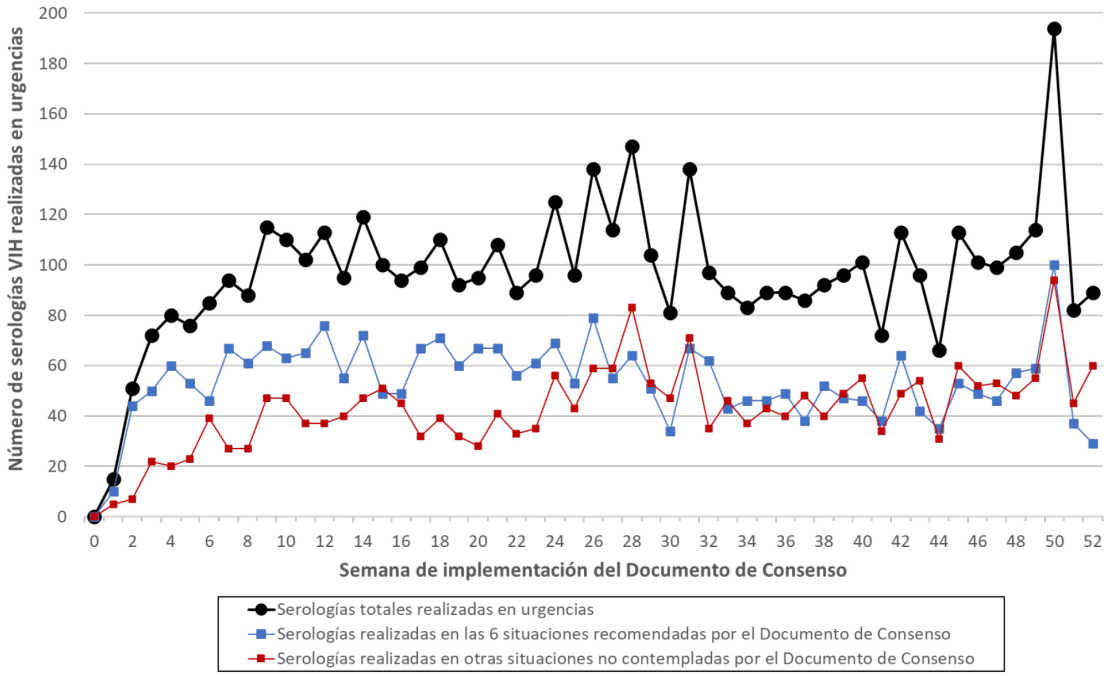

Figura 1 Serologías VIH realizadas en urgencias desde la implementación del Documento de Consenso SEMES-GESIDA

Tabla 1 **Número total de serologías solicitadas y casos detectados detalladas por hospital y por circunstancia que determinó la solicitud.**

	Serologías solicitadas N	Diagnósticos realizados N (%)
Según hospital		
Hospital Clínic (Barcelona)	1.601	16 (1,00)
Hospital Universitari de Bellvitge (L'Hospitalet de Llobregat, Barcelona)	1.037	5 (0,48)
Hospital Fundació Althaia (Manresa, Barcelona)	537	1 (0,19)
Hospital de la Santa Creu i Sant Pau (Barcelona)	513	3 (0,58)
Hospital Doctor Trueta (Girona)	300	1 (0,33)
Hospital Parc Taulí (Sabadell, Barcelona)	279	0 (0)
Hospital Sant Pau i Santa Tecla (Tarragona)	270	2 (0,74)
Hospital Fundació Esperit Sant (Santa Coloma de Gramenet, Barcelona)	244	3 (1,23)
Hospital del Mar (Barcelona)	169	4 (2,37)
Hospital Arnau de Vilanova (Lleida)	157	13 (8,28)
Según circunstancia de la solicitud		
Incluida en el Documento de Consenso	2.841	32 (1,13)
Solicitud de profilaxis post-exposición	1.183	5 (0,42)
Sospecha de infección de transmisión sexual	660	6 (0,91)
Neumonía comunitaria (18-65 años)	610	13 (2,13)
Síndrome monocleósico	230	5 (2,17)
Herpes zóster (18-65 años)	131	1 (0,76)
Práctica de chemsex	27	2 (7,41)
No incluida en el Documento de Consenso	2.266	16 (0,71)
Total	**5.107**	**48 (0,94)**

Aunque la prevalencia resultó superior en las solicitudes que se ajustaban a las circunstancias del DC que a las que no (1,12% frente a 0,71%), dicha diferencia no resultó estadísticamente significativa (p=0,16). Por otro lado, en relación a las circunstancias específicas definidas en el DC, el porcentaje de positividad osciló entre el 7,41% (IC 95%: 0,91-24,3) en los pacientes que consultaron por práctica de *chemsex* y el 0,42% (IC 95%: 0,14-0,98) de los que consultaron solicitando PPE. Como se aprecia en la Figura 2, en todas las situaciones, tanto analizadas de forma agrupada como individualmente, cabe considerar la solicitud de serología VIH en urgencias como eficiente, pues el límite inferior del IC 95% de la estimación siempre fue mayor al 0,1%. La única excepción fue la consulta por herpes zóster. En relación a las solicitudes no definidas en el DC, se detectaron pacientes infectados por VIH en 12 circunstancias diferentes (Tabla 2), y la prevalencia osciló entre la el 10% de serologías positivas en las solicitudes motivadas por linfopenia (1 positivo de 10 determinaciones) y el 0,38% en el caso del estudio de posexposición laboral (1 positivo de 263 determinaciones). Aplicando los mismos criterios de eficiencia que para las circunstancias incluidas en el DC (prevalencia superior al 0,1%), esta condición se cumplía para la linfopenia (10%, IC 95%: 0,25-44,5), fiebre con poliartralgias o poliartritis (7,41%, 0,91-24,3), alteración conductual, confusión o encefalopatía (3,45%, 0,42-11,9) y fiebre de origen desconocido (2,50%, 0,82-5,74) (Figura 2).

DISCUSIÓN

El presente estudio demuestra que la detección de infección por VIH oculta en los SUH en determinadas circunstancias de elevada sospecha clínica, las cuales se consensuaron en un DC de SEMES-GESIDA [15], es posible y eficiente. Además, hemos encontrado que esta estrategia dirigida de solicitud de serología VIH es eficiente tanto de forma general como en prácticamente todas las situaciones en las que los expertos recomendaron que sería de buena práctica clínica realizar dicha solicitud. Finalmente, creemos que es una aportación también relevante el haber detectado una serie de circunstancias, no contempladas en el DC original, en las que es posible que resulte eficiente la implementación de su determinación a los pacientes que consultan en urgencias.

Tabla 2 **Distribución de los motivos de solicitud y resultados de las serologías VIH realizadas en urgencias por otras razones diferentes a los 6 motivos definidos por el Documento de Consenso SEMES-GESIDA.**

	Determinaciones realizadas	Casos diagnosticados	% Prevalencia
Estudio post-exposición laboral	**263**	**1**	**0,38**
Fiebre de origen desconocido	**200**	**5**	**2,50**
Diálisis urgente	155	0	-
Hepatitis	**138**	**1**	**0,72**
Neumonía por COVID-19	116	0	-
Lesión cutánea	82	0	-
Agresión sexual	**69**	**1**	**1,45**
Revisiones del personal de casa	63	0	-
Alteración conductual - Confusión - Encefalopatía	**58**	**2**	**3,45**
Síndrome constitucional	53	0	-
Adenopatía	**50**	**1**	**2,00**
Consumo - Intoxicación por drogas de abuso	**49**	**1**	**2,04**
Plaquetopenia	**47**	**1**	**2,13**
Diarrea crónica	39	0	-
Insuficiencia renal aguda	39	0	-
Sospecha de tuberculosis pulmonar	37	0	-
Lesiones - Infecciones diversas del área genital	35	0	-
Disfagia - Amigdalitis - Lesiones cavidad oral	**34**	**1**	**2,94**
Deterioro cognitivo de debut o subagudo	33	0	-
Dolor abdominal - Colitis - Enteritis	32	0	-
Embarazo o parto	31	0	-
Relaciones sexuales de riesgo (no incluye chemsex ni PPE)	**28**	**1**	**3,57**
Fiebre y poliartralgias o poliartritis	**27**	**2**	**7,41**
Ictus o accidente vascular transitorio	25	0	-
Sepsis	23	0	-
Vasculitis – Enfermedad autoinmune	20	0	-
Astenia	19	0	-
Cirrosis - Hepatopatía crónica	18	0	-
Consultas ginecológicas diversas	18	0	-
Meningoencefalitis	16	0	-
Pancitopenia	16	0	-
Psicosis aguda (no relacionado con drogas)	16	0	-
Anemia	14	0	-
Procedencia de zona endémica	13	0	-
Agresión (no sexual) - Atropello - Politraumatismo	13	0	-
Enfermedad inflamatoria pélvica	12	0	-
Enolismo	12	0	-
Derrame pleural	11	0	-
Pancreatitis aguda	11	0	-
Infección de orina	11	0	-
Esofagitis	11	0	-
Linfopenia	**10**	**1**	**10,00**
Donante de órganos	10	0	-
Lesión intracraneal en la TC craneal	10	0	-
94 procesos en los que se solicitaron menos de 10 determinaciones	279	0	-

Los valores en negrita denotan las circunstancias en las que se detectó algún paciente con serología VIH positiva

TC: tomografía computadorizada; PPE: profilaxis posexposición.

Tabla 3 **Motivos de solicitud en los 48 casos diagnosticados de VIH en urgencias**

Motivo de solicitud de serología VIH en urgencias	Diagnósticos realizados N	Seroprevalenica %
Neumonía comunitaria (18-65 años)	**13**	**2,13**
Sospecha de infección de transmisión sexual	**6**	**0,91**
Solicitud de profilaxis post-exposición	**5**	**0,42**
Síndrome monocleósico	**5**	**2,17**
Fiebre de origen desconocido	5	2,50
Práctica de chemsex	**2**	**7,41**
Fiebre y poliartralgias o poliartritis	2	7,41
Alteración conductual/confusión/encefalopatía	2	3,45
Herpes zóster (18-65 años)	**1**	**0,76**
Estudio post-exposición laboral	1	0,38
Hepatitis aguda	1	0,72
Agresión sexual	1	1,45
Adenopatía	1	2,00
Consumo - Intoxicación por drogas de abuso	1	2,04
Plaquetopenia	1	2,13
Disfagia - Amigdalitis - Lesiones cavidad oral	1	2,94
Relaciones sexuales de riesgo (no incluye chemsex ni PPE)	1	3,57
Linfopenia	1	10,00
Total	**48**	**0,94**

Los líneas en negrita denotan las 6 condiciones definidas en el documento de consenso.

En relación a las solicitudes de serología VIH en los SUH que el programa Urgències VIHgila ha generado durante un año, cabe hacer varias consideraciones. En primer lugar, la meseta se alcanzó de forma relativamente rápida, una vez transcurridos 2 meses desde la implementación del programa (Figura 1). En segundo lugar, resulta llamativo que más del 40% de determinaciones realizadas lo fueron por otras circunstancias diferentes a las definidas en el DC. Claramente, la puesta en práctica de un programa proactivo de determinación serológica del VIH en SUH hace que los profesionales se muestren más atentos a la detección de pacientes VIH en una amplia variedad de circunstancias. De hecho, se observó cómo el número de solicitudes creció en el segundo periodo del estudio. De forma relevante, y tomadas en conjunto, es de destacar que la eficiencia de estas solicitudes "no dirigidas" debe considerarse como eficiente (seroprevalencia detectada: 0,71%, IC 95%: 0,40-1,14). En tercer lugar, nuestros datos confirman que la estrategia de detección selectiva en pacientes que consultan por las 6 circunstancias definidas en el DC de SEMES-GESIDA tiene un rendimiento superior a la encontrada en estrategias de detección universal en los SUH. Efectivamente, mientras que los resultados de un meta-análisis reciente que incluyó 12 estudios que evaluaban esta estrategia mostró una seroprevalencia de 0,60% (IC 95%: 0,39-0,84) [14], en el caso de la detección dirigida propuesta en el DC esta seroprevalencia ha sido casi del doble (1,12%, IC 95%:0,77-1,58). Finalmente, es posible que aún exista margen de mejora en cuanto al número de solicitudes que se realizan, especialmente para alguna circunstancia en particular, como puede ser el caso del herpes zóster, donde se registró un número relativamente bajo de serologías (131, un promedio de 1 por SUH y mes). La extensión global de esta infradeterminación no se determinó en el presente estudio. No obstante, aun considerando que solo se hubiesen realizado en una cuarta parte de todas las determinaciones (hipotéticamente, las que correspondiesen a los pacientes con mayor sospecha de infección por VIH por determinados elementos de la historia clínica) y que el resto de casos en los que no existió solicitud hubiesen sido todos negativos, nuestros datos indican que la estrategia del DC SEMES-GESIDA sigue siendo eficiente, ya que la prevalencia de seropositividad en esta teórica situación sería de 0,26% (IC 95%: 0,18-0,38), con un límite inferior del IC 95% por encima del 0,1% que define la eficiencia.

Sobre los motivos específicos de solicitud contemplados en el DC, la prevalencia más alta de seropositividad se registró

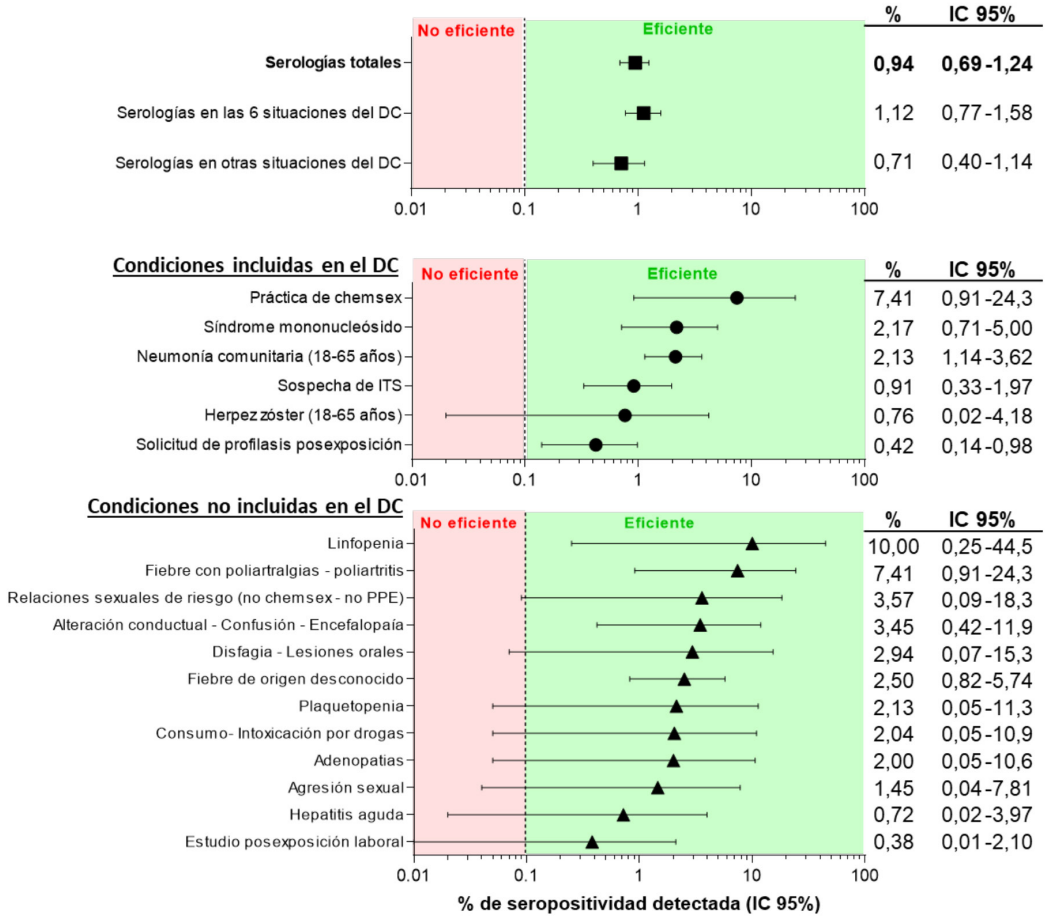

Figura 2 **Estimación (en porcentajes e intervalos de confianza del 95%) de la prevalencia de infección por VIH no conocida en cada uno de los grupos de estudio (el eje de abscisas se expresa en formato logarítmico)**

DC: documento de consenso; PPE: profilaxis post-exposición; ITS: infección de transmisión sexual; IC: intervalo de confianza

para los pacientes que consultaron por problemas derivados de la práctica de *chemsex*, que se estimó en un 7,41%. No sorprende, pues, esta es una circunstancia bien conocida de alto riesgo, no solo de positividad al ser consumidores de drogas, sino también de transmisión por las propias condiciones de la práctica de *chemsex* [16-20]. Aunque esta circunstancia solo se dé en determinadas zonas y ciertos SUH (en nuestro caso, los dos diagnósticos procedían del mismo SUH), los SUH deben estar especialmente vigilantes a ella, pues las consultas de este grupo de pacientes se realizan mayoritariamente en ellos y no en otros puntos de la red asistencial. En relación al grupo de circunstancias en las que se estimó una prevalencia intermedia, entre el 0,8% y el 2,2%, todas ellas son circunstancias que estudios previos han relacionado de forma clara con una mayor prevalencia de VIH: síndrome mononucleósido, ITS, neumonía adquirida en la comunidad o herpes zóster [21-24]. Por ello, no resulta sorprendente que todas ellas alcanzaran criterios de eficiencia, excepto el diagnóstico de herpes zóster en pacientes entre 18 y 65 años. Aun en este caso, la estimación de prevalencia puntual fue del 0,76%, aunque debido al bajo número de determinaciones realizadas el IC 95% fue amplio e incluyó la posibilidad de una seroprevalencia en la población por debajo del 0,1%, que define la eficiencia de acuerdo con publicaciones previas [16]. Creemos que en este caso es posible que se haya incurrido en un error estadístico de segunda especie, y que el bajo número de determinaciones haya hecho que el poder estadístico no haya sido suficiente para poder alcanzar la significación, como ha sucedido en estudios similares que han incluido un número limitado de pacientes [25]. Finalmente, incluso el escenario con una seroprevalencia más baja, el de PPE, los datos obtenidos indican la necesidad de este proceder. Probablemente la prevalencia incrementada se deba a que una parte de pacientes que acuden solicitando PPE se trate de personas con múltiples parejas sexuales y con prácticas sexuales de riesgo repetidas. Numerosos estudios han mostrado la importancia de una buena aproximación a este colectivo en el que, más allá de valorar convenientemente en los SUH el riesgo de la exposición y facilitar la profilaxis, debe realizarse

una serología VIH por tratarse de un colectivo de riesgo [26-28]. Por tanto, el presente estudio llama a la acción a todos los SUH, a los gestores hospitalarios y a las administraciones para que pongan en marcha las medidas que permitan generalizar en España las recomendaciones del DC SEMES-GESIDA. Una aproximación al impacto epidemiológico y económico que ello tendría en España ha mostrado que una inversión de 20 millones de euros en 20 años evitaría 13.615 nuevas infecciones en comparación con la actual estrategia de diagnóstico. Esta reducción de la incidencia de VIH supondría un ahorro potencial de 4.411 millones de euros en 2 décadas, con un retorno económico de 224 euros por cada euro invertido [29].

Finalmente, comentar que se detectaron hasta 138 motivos diferentes para solicitar una serología VIH en urgencias aparte de las 6 situaciones consensuadas por los expertos en 2020 [15]. Creemos que ello es positivo, pues el abanico de situaciones en las que el riesgo de padecer una infección por VIH está incrementado son muchas y nuestros resultados así lo ilustran: hasta en 12 circunstancias diferentes se diagnosticaron casos de infección por VIH no conocida hasta entonces. Sin embargo, en muchas circunstancias no se detectaron casos positivos, un dato que pudiera resultar llamativo como por ejemplo entre los pacientes procedentes de zonas endémicas (tal vez por el modelo de cobertura universal español y el buen control de estos pacientes por la atención primaria) o pacientes con tuberculosis (tal vez por el bajo número de casos analizados). Por otro lado, algunos motivos de solicitud en los SUH no son discrecionales para el especialista en urgencias, sino que constituyen una obligación legal (donación de órganos, agresión sexual) o clínica (inicio de diálisis, punción accidental) bien establecida. La pertinencia de dicha solicitud queda bien demostrada en el presente estudio, en el que se detectó un caso positivo en una agresión sexual y uno en una PPE accidental. Con todo, la prevalencia de seropositivos resultó muy elevada en algunas circunstancias, como es el caso de la linfopenia, la fiebre con poliartralgias o poliartritis, la detección de relaciones sexuales de riesgo (aunque el paciente no consultase por *chemsex* o PPE) o la alteración conductual, confusión o encefalopatía, todas ellas por encima del 3%. De hecho, tomando el mismo criterio de eficiencia que para las condiciones del DC (>0,1% de prevalencia), hemos encontrado que este criterio se cumplía para 4 condiciones: linfopenia, fiebre con poliartralgias o poliartritis, alteración conductual, confusión o encefalopatía y fiebre de origen desconocido. Sin embargo, este hallazgo debe tomarse con cautela, porque si bien la intervención del programa Urgències VIHgila hizo que probablemente en muchos de los pacientes que cumplían las condiciones del DC la serología se realizase, probablemente no sucedió lo mismo con el resto de condiciones, pues la solicitud se realizó a criterio del especialista en urgencias, cuya sensibilidad varió entre profesionales y entre SUH. Con todo, supone un buen punto de partida para investigar de forma dirigida si realmente estas condiciones tienen la eficiencia suficiente para incorporarse a futuros documentos de consenso.

Una consideración relevante de nuestro estudio es que los buenos resultados de este modelo de diagnóstico precoz del VIH, sin duda rentabilísimo, se han alcanzado en un ámbito asistencial geográfico concreto, Cataluña, y mediante el patrocinio de la colaboración con la industria. Entre los puntos destacables con los que cuenta el programa "Urgències VIH gila", creemos que para la consecución de estos resultados ha resultado fundamental la presencia de una encargada del proyecto, externa e independiente a los coordinadores del proyecto y de los Champions de los centros, que actúa como data manager y dinamizadora social, registrando y actualizando los resultados semanalmente y centro por centro. Resulta, pues, obligado trasladar a las administraciones pertinentes la necesidad de que exista esta estructura, específicamente dirigida a esta tarea, si se quieren remedar nuestros resultados en otras comunidades o en escenarios en los que no exista la colaboración de la industria. Incluso en Cataluña, el futuro de este programa cuando la industria deje de prestar su apoyo es dudoso. Por tanto, creemos que es fundamental el apoyo directo desde el Sistema Nacional de Salud y las administraciones implicadas si realmente quieren que un programa como este se generalice en el territorio y se perpetúe en el tiempo, ya que el diagnóstico tardío sigue siendo uno de las principales causas de la expansión de esta pandemia en el mundo y en España.

Limitaciones. En primer lugar, no se ha documentado el grado de cumplimiento de las recomendaciones del DC, y es posible que para alguna circunstancia no se hayan alcanzado porcentajes cercanos al 100%. Sin embargo, como se ha comentado anteriormente, aun cuando este porcentaje hubiese sido de solo el 25%, la estrategia propuesta por el Documento de Consenso SEMES-GESIDA hubiese resultado eficiente. Segundo, los datos que sugieren que algunas otras circunstancias también pueden resultar eficientes son solo generadores de hipótesis, porque en estos casos no estaba protocolizada su solicitud y, por tanto, el sesgo de solicitarlo solo en pacientes altamente sospechosos de ser seropositivos por otras razones es muy alto. Además, los resultados de la implementación del DC en Cataluña podrían no ser los mismos en otras comunidades autónomas. Por un lado, la diferente prevalencia de VIH no conocido en cada comunidad puede hacer el programa más exitoso (y por ende, más necesario) en comunidades de alta prevalencia. Por último, es importante la predisposición de los SUH a implementar una medida que no tiene una repercusión asistencial inmediata para el motivo de consulta actual del paciente en urgencias. Así, una encuesta previa a todos los SUH españoles mostró que los ubicados en Cataluña se encontraban entre los de mayor predisposición a implicarse en la detección activa en sus SUH [30] y esto puede haber ayudado a la obtención de los buenos resultados del proyecto Urgències VIHgila que aquí se presentan.

Conclusión. Los resultados iniciales del programa "Urgències VIHgila", que desarrolla una estrategia estructurada encaminada a implementar la determinación de serología VIH en los SUH en los procesos previamente definidos en el DC SEMES-GESIDA, muestra que esta determinación es eficiente, tanto de forma global como para casi todos los procesos evaluados de forma individualizada. Además, se han identificado algunos procesos adicionales que podrían ser añadidos a los

previamente contemplados para aumentar la rentabilidad de esta estrategia, si bien deberán ser investigados de forma controlada para confirmar los indicios aquí encontrados. Todo ello permite concluir que una inversión más amplia en este sentido permitiría alcanzar una elevada eficiencia y contribuir a la contención y erradicación de la pandemia por VIH.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Estudio epidemiológico sobre el impacto de la vacunación antigripal en la evolución clínica de pacientes con COVID-19 y la coinfección por ambos virus en Gran Canaria, España

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RESUMEN

Objetivo. Analizar la frecuencia de coinfecciones entre los virus gripales y el SARS-CoV-2, además de las diferencias en la evolución (riesgo de mortalidad, ingreso hospitalario o en intensivos) de los pacientes infectados por el virus del SARS-CoV-2 según vacunación o no vacunación de la gripe en la temporada 2021-2022.

Método. Estudio retrospectivo observacional de base poblacional en una cohorte de 19.850 pacientes diagnosticados de COVID-19 entre el 1 de junio de 2021 y 28 de febrero de 2022 en la isla de Gran Canaria.

Resultados. Fueron vacunados de la gripe 1.789 personas, el 9% del total de pacientes diagnosticados de COVID-19. 13.676 personas (68,9%) contaban con pauta completa de vacunación del COVID-19. En el periodo comprendido entre el 1 de junio de 2021 y 28 de febrero de 2022 se registraron 8 casos de coinfección gripe y COVID-19. Hipertensión (18,5%), asma (12,8%) y diabetes (7,2%) fueron las comorbilidades más frecuentes. Hubo 147 defunciones (0,7%). Las personas de mayor edad ([OR] 1,11 IC 95% 1,09-1,13) y con cáncer ([OR] 4,21 IC 95% 2,58-6,89) tuvieron mayor riesgo de fallecer por COVID-19 (p<0,05). El sexo femenino fue considerado un factor protector ([OR] 0,61 IC 95% 0,40-0,92).

Conclusiones. La edad avanzada, el sexo masculino y el cáncer fueron factores pronósticos independientes de mortalidad. Tres dosis de la vacuna del SARS-CoV-2 y la vacuna de la gripe fueron altamente efectivas para prevenir muertes e ingresos relacionados con COVID-19. Estos hallazgos sugieren que la vacunación contra la gripe puede ayudar a controlar la pandemia.

Palabras clave: COVID-19, gripe, vacunas, infección, inmunidad.

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Epidemiological study on the impact of influenza vaccination on the clinical course of patients with COVID-19 and co-infection by both viruses in Gran Canaria, Spain

ABSTRACT

Objectives. To analyze the frequency of influenza and SARS-CoV-2 co-infections, as well as the differences in the course of disease (risk of mortality, hospital and intensive care admissions) in patients infected with the SARS-CoV-2 virus in relation to flu vaccination status in the 2021-2022 season.

Methodology. Population-based observational retrospective study in a cohort of 19,850 patients diagnosed with COVID-19 between June 1, 2021 and February 28, 2022 on the island of Gran Canaria.

Results. A total of 1,789 patients (9%) diagnosed with COVID-19 had received flu vaccinations. 13,676 people (68.9%) had a full course of COVID-19 vaccinations. In the period between June 1, 2021 and February 28, 2022, 8 cases of flu and COVID-19 coinfection were recorded. Hypertension (18.5%), asthma (12.8%) and diabetes (7.2%) were the most frequent comorbidities. There were 147 deaths (0.7%). Older patients ([OR] 1.11 95% CI 1.09-1.13) and people with cancer ([OR] 4.21 95% CI 2.58-6.89) had a higher risk of dying from COVID-19 (p<0.05). Female sex was noted as a protective factor ([OR] 0.61 95% CI 0.40-0.92).

Conclusions. Old age, male sex and cancer were independent prognostic factors for mortality. Three doses of SARS-CoV-2 vaccines and influenza vaccines were highly effective in preventing COVID-19-related deaths and hospital admissions. These findings suggest that flu vaccination can help control the pandemic.

Keywords: COVID-19, flu, vaccines, infection, immunity.

INTRODUCCIÓN

Desde diciembre de 2019 la enfermedad por coronavirus 2019 (COVID-19) ha sido una emergencia de salud pública internacional [1]. En todo el mundo ha habido más de 636 millones de casos de COVID-19 y más de 6,6 millones de muertes a 3 de noviembre de 2022 [2].

El coronavirus del síndrome respiratorio agudo grave de tipo 2 (SARS-CoV-2) imita el virus de la influenza en cuanto a la presentación clínica, mecanismo de transmisión y coincidencia estacional. Por lo tanto, la coinfección por ambos virus es factible [3].

La gripe es una enfermedad de etiología viral que se presenta como epidemias anuales en los meses invernales y de forma pandémica de manera ocasional. Aunque en general es una enfermedad leve y autolimitada, cuando afecta a población de edad avanzada o con patologías crónicas puede aumentar la mortalidad [4,5].

La estrategia más efectiva para prevenir la enfermedad por el virus influenza es la vacunación, mitigando la carga sobre los sistemas de salud. Sin embargo, ha sido un desafío mantener los servicios de vacunación contra el virus influenza durante la pandemia por SARS-CoV-2 al haber tenido ésta el potencial de interrumpir los programas de vacunación en muchos países [6]. Por otro lado, las medidas para reducir la transmisión de SARS-CoV-2 también han sido efectivas para reducir la transmisión de otros virus respiratorios endémicos [7,8].

La efectividad vacunal frente a infección confirmada por laboratorio fue moderada (50-60%) frente al a los virus A(H1N1) pdm09 y B, y baja o nula, dependiendo del grupo de edad, frente al virus A(H3N2). Se ha estimado un impacto muy positivo del programa de vacunación antigripal en España en la temporada 2019-20 entre los mayores de 64 años. La vacuna antigripal fue capaz de prevenir en este grupo de edad un 26% de hospitalizaciones, un 40% de admisiones en UCI (Unidades de Cuidados Intensivos) y un 37% de defunciones por todas las causas atribuibles a gripe que ocurren en hospitales [9]. La coinfección con virus de influenza se asoció con mayores probabilidades de recibir ventilación mecánica invasiva en comparación con la monoinfección por SARS-CoV-2 [10].

Este estudio analizó las características epidemiológicas y clínicas de los casos de COVID-19 vacunados de la gripe en Gran Canaria. Se analizaron las posibles diferencias en la evolución (ingreso hospitalario, ingreso en UCI y mortalidad) de los pacientes infectados por el virus del SARS-CoV-2 vacunados y no vacunados de la gripe en la temporada 2021-2022. Se determinó la frecuencia de coinfecciones entre los virus gripales y el SARS-CoV-2.

MÉTODOS

Tipo de estudio. Estudio retrospectivo observacional de base poblacional en una cohorte de 19.850 pacientes de 12 o más años de edad diagnosticados de COVID-19 entre el 1 de junio de 2021 y el 28 de febrero de 2021 en Gran Canaria.

Criterios de inclusión. Caso COVID-19 confirmado: paciente que cumple criterio clínico de caso sospechoso con PDIA (prueba diagnóstica de infección activa) positiva, o bien, paciente asintomático con PDIA positiva e IgG negativa o no realizada. Caso sospechoso: paciente con infección respiratoria aguda de aparición súbita de cualquier gravedad que cursa con fiebre, tos o disnea. Otros síntomas como odinofagia, anosmia, ageusia, dolor muscular, diarrea, dolor torácico o cefalea, entre otros, se consideraron también síntomas de sospecha. El criterio de exclusión fue edad <12 años.

Obtención y fuente de los datos. Se han identificado todos los pacientes vacunados frente al SARS-CoV-2 en Gran Canaria (periodo 28 de diciembre de 2020 a 31 de diciembre de 2021) mediante el registro REGVACU (Registro de Vacunación frente al SARS-CoV-2 en España). Se identificaron todos los casos de COVID-19 en Gran Canaria notificados a ReVeCa (Red de Vigilancia Epidemiológica de Canarias) en el periodo comprendido entre el 1 de junio de 2021 y el 28 de febrero de 2022). La información clínica de los pacientes diagnosticados de COVID-19 y su estatus de vacunación antigripal se obtuvo de la historia clínica electrónica de Atención Primaria, DRAGO-AP.

Se consideró como vacunación antigripal a aquella persona que ha recibido una dosis de vacuna frente a la gripe en la temporada estacional indicada. La campaña de vacunación contra la gripe de la temporada 2021-2022 comenzó en Canarias el 28 de octubre de 2022. Los grupos diana fueron: mayores de 60 años, embarazadas, enfermos crónicos de cualquier edad, personal sanitario y cuidadores de personas vulnerables.

Variables. La principal variable de resultado fue la mortalidad. La vacunación antigripal fue la principal variable independiente. Covariables de control fueron: edad, sexo, comorbilidades subyacentes (asma, cáncer, demencia, diabetes, enfermedad coronaria, Enfermedad Pulmonar Obstructiva Crónica o EPOC, Insuficiencia Cardiaca Congestiva o ICC, hipertensión arterial o HTA y obesidad), tratamiento inmunosupresor, fechas de la primera, segunda y dosis de refuerzo o booster de la vacuna del COVID-19 y tipo de vacuna (Pfizer, Moderna, Astrazeneca, Janssen).

Definiciones. Se clasificó como diabetes: glucemia basal ≥126 mg/dl o con tratamiento antidiabético; obesidad: IMC ≥30 kg/m^2; HTA: presión arterial sistólica ≥140 mmHg y/o presión arterial diastólica ≥90 mmHg, o con tratamiento antihipertensivo.

Pauta vacunal completa para COVID-19. Paciente que haya recibido 2 dosis de vacuna distanciadas un mínimo de 19 días si la primera dosis fue BNT162b2 ARNm (Pfizer-BioNTech), 21 días tratándose de ChAdOx1 nCoV-19 (AstraZeneca-Universidad Oxford) o 25 días tratándose de ARNm-1273 (Moderna), y que haya transcurrido un mínimo desde la última dosis de 7 días si la última dosis fue de Pfizer, o 14 días si fue de AstraZeneca o Moderna. También se consideraron completamente vacunadas aquellas personas que recibieron una dosis de Ad26.COV2.S (Janssen) hace más de 14 días y aquellas de ≤65 años

que habiendo pasado la enfermedad han recibido una dosis de cualquier vacuna, superado el periodo mínimo igual al establecido para las segundas dosis. En la pauta heteróloga en la que se utiliza AstraZeneca en primera dosis y vacunas ARNm en segunda, se consideró completamente vacunado tras 7 días si la segunda dosis fue con Pfizer, o 14 días si fue con Moderna [11].

Análisis estadístico. Se realizó análisis descriptivo de los resultados utilizando medidas de frecuencia y porcentajes para las variables categóricas. El análisis bivariante para las variables cualitativas se realizó mediante la prueba de la χ^2, utilizando la razón de verosimilitud (Likelihood Ratio) cuando fue necesario. El nivel de significación estadística utilizado fue el 5% (p<0,05). El tratamiento estadístico de los datos se realizó mediante la aplicación estadística Statistical Package for the Social Sciences (SPSS), v28.

Estudio aprobado por el comité de Ética para la Investigación Clínica del Hospital Universitario de Gran Canaria Dr. Negrín (número de registro 2021-356-1 COVID19). Se llevó a cabo de acuerdo con las leyes y reglamentos locales, con la Declaración de Helsinki, Fortaleza y las Buenas Prácticas Clínicas.

RESULTADOS

En el periodo comprendido entre el 1 de junio de 2021 y el 31 de diciembre de 2021 se vacunaron de la gripe 1.789 personas (9,0%) del total de pacientes diagnosticados de COVID-19. 13.676 personas (68,9%) fueron vacunadas con la pauta completa de COVID-19.

En el periodo comprendido entre el 1 de junio de 2021 y 28 de febrero de 2022 se registraron 8 casos de coinfección gripe y SARS-CoV-2. En la figura 1 se muestra la descripción de estas coinfecciones según las covariables analizadas.

En la tabla 1 se muestra el análisis bivariable entre vacunación antigripal y las principales covariables del estudio. El sexo femenino, los grupos de población de mayor edad (≥70 años), las personas en tratamiento inmunosupresor y las que precisaron ingreso hospitalario se asociaron a mayor tasa de vacunación antigripal.

En el modelo de regresión logística multivariable (tabla 2) encontramos que las personas de mayor edad, hombres y con cáncer, tenían mayor probabilidad de fallecer por COVID-19. Otras variables asociadas a mayor probabilidad de defunción fueron el ingreso hospitalario y precisar ventilación mecánica durante el ingreso (p<0,05). La tercera dosis de la vacuna contra el SARS-CoV-2 se asoció a menor riesgo de fallecer (Odds Ratio 0,17, IC 95% 0,08–0,35; p< 0,05), también fue protectora la vacuna antigripal (Odds Ratio 0,36, IC 95% 0,17–0,78; p< 0,05). No se encontró asociación con asma, EPOC, HTA, obesidad, diabetes, pauta de vacunación completa contra el virus del SARS-CoV-2 o ingreso en UCI (p>0,05).

DISCUSIÓN

Se observó que la evolución de la temporada de gripe 2021-22 fue más similar a la temporada inmediatamente anterior 2020-21, que a las temporadas más lejanas. Desde el comienzo de la temporada y a 28 de febrero de 2022 se encontraron 142 virus de la Gripe: 136 son Virus A [96 (AH3), 1 (AH3N2), 17 (AH1pdm09), 4 (AH1N1pdm09) y 23 (ANS)]. Solo se encontró un virus B [12].

En la temporada 2020-2021 se vacunaron en Canarias 492.889 personas, un 71,8% de la población diana [13]. Se espera que esta cifra sea similar en la temporada 2021-22 [14]. A medida que se levanten las restricciones de salud pública es más probable que ocurran coinfecciones de virus respiratorios, entre ellos el SARS-CoV-2 [10]. No ha podido demos-

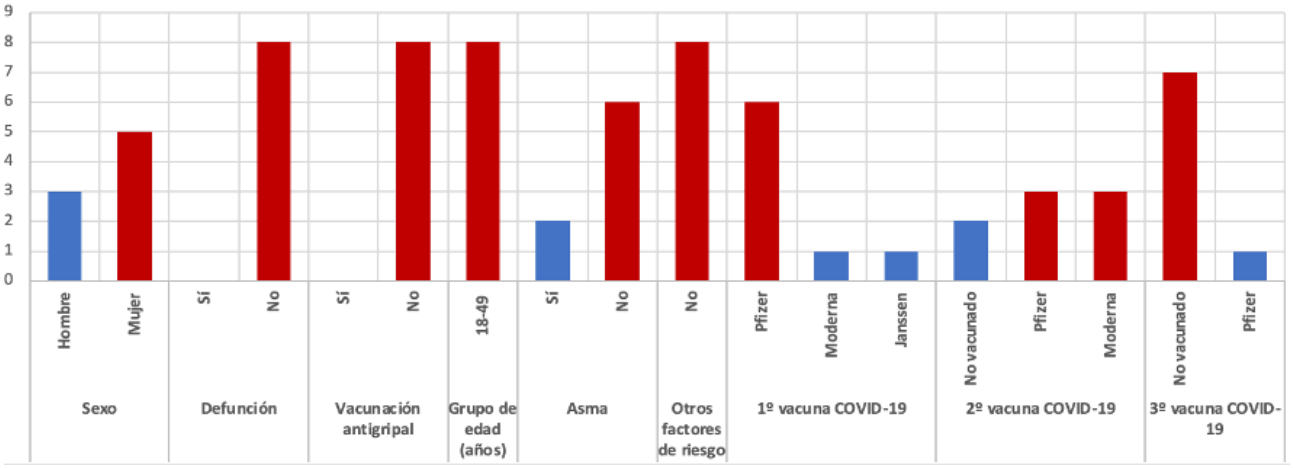

Figura 1 Descripción de la frecuencia de coinfecciones por el virus de la gripe y del SARS-CoV-2 (n=8).

Tabla 1 **Análisis bivariable. Asociaciones entre las principales covariables del estudio y la vacunación antigripal en 1.789 personas vacunadas de un total de 19.850 participantes.**

Variables	N casos	Vacunación gripe SÍ (%)	Vacunación gripe NO (%)	Odds Ratio (IC)	P valor
Sexo					
Hombre	9.344	727 (7,8)	8.617 (92,2)	1	0,000
Mujer	10.506	1062 (10,1)	9.444 (89,9)	1,33 (1,21 -1,47)	
Defunciones					
Si	147	11 (7,5)	136 (92,5)	0,82 (0,44-1,51)	0,516
No	19.703	1.778 (9)	19.725 (91)	1	
Grupos de edad					
18-49	13.884	533 (3,8)	13.351 (96,2)	0,01 (0,00-0,01)	0,000
50-69	4.619	712 (15,4)	3.907 (84,6)	0,11 (0,07-0,15)	0,000
>=70	1.347	544 (40,4)	803 (59,6)	1	Ref
Ventilación mecánica					
Si	60	7 (11,7)	53 (88,3)	1,34 (0,61-2,94)	0,472
No	19790	1782 (9)	18.008 (91)	1	
Ingreso en Unidad de Cuidados Intensivos					
Si	208	22 (10,6)	186 (89,4)	1,20 (0,77-1,87)	0,428
No	19642	1767 (9)	17.875 (91)	1	
Ingreso hospitalario					
Si	831	138 (16,6)	693 (83,4)	2,10 (1,73-2,53)	0,000
No	19.019	1.651 (8,7)	17.368 (91,3)	1	
Tratamiento inmunosupresor					
Si	330	84 (25,5)	246 (74,5)	3,57 (2,77-4,59)	0,000
No	19.520	1.705 (8,7)	17.815 (91,3)	1	

trarse definitivamente si estas coinfecciones determinan una mayor gravedad de la COVID-19. El estudio inicial de Ding et al [15] sobre infecciones mixtas SARS-CoV-2/gripe no mostró empeoramiento o peor pronóstico que la infección en solitario. Sin embargo, un amplio estudio del Servicio de Salud Pública inglés demostró que, a pesar de que las coinfecciones son escasas, los pacientes coinfectados con ambos virus presentan 2,4 veces más riesgo de fallecer que los que se infectan sólo por uno, dato especialmente relevante en >65 años entre los cuales fallecen más del 50% de los coinfectados [16]. Estos datos apoyan la necesidad de proteger a la población en general, especialmente a los grupos de riesgo, para evitar posibles coinfecciones («la tormenta perfecta»), que parecen incrementar significativamente la morbilidad y mortalidad [17]. De acuerdo con esta hipótesis, Marín-Hernández et al [18] han estudiado la relación entre vacunación antigripal en >65 años y evolución de la COVID-19 en Italia, hallando una intensa correlación entre mayor porcentaje de vacunación y menor número de fallecidos por COVID-19. Otro amplio estudio realizado en Italia demuestra una asociación inversa significativa entre cobertura vacunal frente a la gripe, tasa de seroprevalencia poblacional frente al SARS-CoV-2 (difusión de la infección), prevalencia de pacientes hospitalizados, ingresos en UCI y número de fallecimientos atribuibles al virus, estimando que un aumento del 1% en la cobertura vacunal de personas >65 años evitaría 350 ingresos hospitalarios y 2.000 fallecimientos en el país [19]. Otro estudio realizado en Brasil sobre 90.000 pacientes diagnosticados de COVID-19, 31,1% vacunados frente a la gripe, confirmó que los vacunados antes o durante la epidemia del SARS-CoV-2 presentaron menor mortalidad y menos ingresos en UCI [20].

Una posible explicación sería que la vacuna antigripal protegiera parcialmente frente a la infección por SARS-CoV-2. Ello ocurriría si la vacuna estimulara la inmunidad innata frente a otros virus respiratorios. El sistema inmune local respiratorio provocaría una intensa y rápida respuesta que dificultaría otras infecciones víricas respiratorias [5]. Desde el punto de vista inmunológico, la vacuna antigripal está diseñada para inducir una respuesta adaptativa de larga duración mediante la producción de anticuerpos neutralizantes y células T de respuesta. A pesar de la escasa similitud genética entre los virus gripales y el SARS-CoV-2, es posible que algunos linfocitos T-CD8+ reconozcan epítopos menores presentes en ellos. Sin embargo, debido a la extraordinaria diversidad antigénica de los virus gripales, la producción de anticuerpos neutralizantes y de células T frente a otros virus ARN, incluido el SARS-CoV-2, parece poco probable [21]. Por ello, según Fink et al [20], el mecanismo más probable de los posibles beneficios de la va-

Tabla 2 **Análisis multivariable. Asociaciones de mortalidad en las 1.789 vacunados de la gripe entre la población de 19.850**

Variable	Muerte y análisis de regresión logística (IC95%)	P valor
Sexo		
Mujer	0,61 (0,40-0,92)	0,000
Hombre	1 (Ref.)	
Edad (años)	1,11 (1,10-1,13)	0,000
Asma		
Sí	1,17 (0,62-2,20)	0,635
No	1 (Ref.)	
Cáncer		
Sí	4,21 (2,58-6,89)	0,000
No	1 (Ref.)	
Diabetes		
Sí	0,92 (0,59-1,45)	0,722
No	1 (Ref.)	
Enfermedad pulmonar obstructiva crónica		
Sí	0,67 (0,34-1,34)	0,261
No	1 (Ref.)	
Hipertensión arterial		
Sí	1,05 (0,66-1,65)	0,843
No	1 (Ref.)	
Obesidad		
Sí	0,64 (0,13-3,13)	0,585
No	1 (Ref.)	
Pauta de vacunación completa		
Sí	0,82 (0,52-1,32)	0,419
No	1 (Ref.)	
Booster		
Sí	0,17 (0,08-0,35)	0,000
No	1 (Ref.)	
Vacuna de la gripe		
Sí	0,36 (0,17-0,78)	0,010
No	1 (Ref.)	
Ingreso hospitalario		
Sí	15,95 (9,57-26,56)	0,000
No	1 (Ref.)	
Ventilación mecánica		
Sí	4,30 (1,57-11,82)	0,005
No	1 (Ref.)	
Ingreso en Unidad de Cuidados Intensivos		
Sí	1.64 (0,88-3,07)	0,122
No	1 (Ref.)	

cunación sería la inmunidad innata inducida por ella. Además, algunas vacunas, probablemente también la antigripal, inducen mecanismos inmunoterapéuticos no específicos que incrementan la respuesta del huésped frente a otros patógenos a través de un proceso complejo denominado «entrenamiento inmune» (trained immunity) [5].

Otra explicación no virológica al efecto protector de la vacuna antigripal podría ser que los porcentajes más elevados

de vacunación se dieran en estratos socioeconómicos elevados, que presentaran un mejor estado previo de salud. También es posible que esta correlación se deba al azar o al comportamiento epidemiológico de otros virus respiratorios [18].

La vacunación antigripal debe seguir implementándose e intensificarse ya que reduce la prevalencia de la enfermedad, la gravedad de sus síntomas y disminuye hospitalizaciones e ingresos en UCI; aliviando la presión asistencial en todo el ámbito sanitario y permitiendo una mejor atención hacia enfermos con otras patologías. Dada la escasa experiencia en la vacunación antigripal de enfermos de COVID-19, es recomendable que aquellas personas que presenten sintomatología compatible o confirmación de laboratorio para el SARS-CoV-2, retrasen la vacunación antigripal hasta que se hayan recuperado totalmente, recordándoles la necesidad de incorporarse posteriormente al programa vacunal [18, 22, 23]. En definitiva, la vacunación antigripal anual sigue siendo la mejor y, quizás, única herramienta costo-efectiva de salud pública, con un impacto demostrado sobre la epidemiología y prevención de la gripe estacional. Otros autores proponen aumentar las tasas de vacunación antigripal para evitar la coinfección de la gripe con SARS-CoV-2 [24].

Kuderer NM et al [25] indicaron una asociación entre el cáncer y tasas de mortalidad más elevadas. Los pacientes con cáncer pueden estar inmunocomprometidos debido a la terapia antineoplásica, medicamentos de apoyo y las propiedades inmunosupresoras del propio cáncer. Estos hallazgos son congruentes con los resultados de nuestro estudio en el que la prevalencia del cáncer activo como comorbilidad entre los pacientes diagnosticados con COVID-19 fue del 3,2%, identificándose en el análisis multivariable como un factor independiente asociado a la mortalidad.

Los pacientes vacunados son los de mayor edad y comorbilidad, factores que se asocian a una mayor mortalidad en los pacientes COVID-19 sin influir la vacunación antigripal. Múltiples estudios encontraron la edad como un factor de riesgo independiente de mortalidad en pacientes COVID-19, que podría explicarse por la inmunosenescencia [26]. En concordancia con otros estudios, nuestros pacientes con elevada comorbilidad presentaron una mortalidad significativamente mayor que aquellos con comorbilidad baja [27].

Nuestro estudio tiene algunas limitaciones. No hemos incluido datos analíticos que podrían asociarse a una mayor mortalidad como sugieren diversos estudios [9], pero nuestro objetivo era valorar la vacunación antigripal y otras comorbilidades en el riesgo de mortalidad en pacientes diagnosticados de COVID-19. Tampoco se han tenido en cuenta los tratamientos administrados durante el ingreso hospitalario, por su heterogeneidad y escaso nivel de evidencia en estudios publicados [28]. Adicionalmente, la situación epidemiológica puede haber condicionado los criterios de ingreso y disponibilidad de camas y haber influido en los resultados de mortalidad [29].

En este sentido, el Gripómetro (herramienta de conocimiento de la cobertura de vacunación antigripal en tiempo real) se presenta como una herramienta práctica y de gran utilidad que puede ser especialmente importante en momentos como el 2021-2022 y sucesivas temporadas, en las que la gripe podría coexistir con la COVID-19. La vacuna antigripal es un arma clave complementaria, en el contexto de crisis sanitaria del COVID-19, para evitar un posible colapso de la atención sanitaria [30].

En conclusión, la edad avanzada, el sexo masculino, la ausencia de dosis de refuerzo de la vacuna del COVID-19, el ingreso hospitalario o en UCI, la ausencia de la vacuna de la gripe y el cáncer fueron factores pronósticos independientes de mortalidad lo que podría ayudar a los médicos a identificar los pacientes con mal pronóstico para su manejo y tratamiento. Se justifican más estudios sobre el papel de la vacunación de la gripe en el transcurso de la enfermedad por COVID-19, que serán vitales para la investigación y el desarrollo de una vacuna más eficaz. A todas las personas elegibles se les debe ofrecer la vacunación, incluidos aquellos con infección previa por SARS-CoV-2, para reducir su riesgo de infección futura.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Vitamin C and thiamine for the treatment of refractory septic shock in surgical critically ill patients: a retrospective before-and-after study

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ABSTRACT

Introduction. This study aimed to evaluate whether early vitamin C and thiamine administration was associated with a lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock.

Patients and methods. We performed a retrospective before-and-after study on patients with refractory septic shock. According to local protocol, hydrocortisone is initiated in case of refractory septic shock. In January 2017, the protocol was changed and vitamin C and thiamine were included. Patients who were admitted in 2015-2016 and 2017-2018 were included in the control and treatment groups, respectively. The primary end point was 28-day and in-hospital mortality. Secondary end points were ICU mortality, ICU and hospital length of stay, duration of vasopressors and mechanical ventilation, use of renal replacement therapy (RRT), and the modification in serum procalcitonin and SOFA score during the first 72 h.

Results. A total of 120 patients were included (58 in the treatment group and 62 in the control group). Log-rank test in Kaplan-Meier curves showed lower 28-day and in-hospital mortality over time in the treatment group (p=0.021 and p=0.035, respectively) but it not reached statistical significance in ICU mortality over time (p=0.100). The need of RRT was less frequent in treatment group (17.2% vs. 37.1%, p=0.024). There were no differences in other secondary outcomes.

Conclusions. Intravenous vitamin C and thiamine administration in surgical patients with refractory septic shock may be associated with a lower 28-day and in-hospital mortality. Further prospective studies are needed in refractory septic shock.

Keywords: septic shock; vitamin C; thiamine; mortality; vasopressor

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Vitamina C y tiamina para el tratamiento del shock séptico refractario en pacientes críticos quirúrgicos: un estudio retrospectivo antes-después

RESUMEN

Introducción. El objetivo de este estudio fue evaluar si la administración precoz de vitamina C y tiamina estaba asociada a una reducción en la mortalidad a los 28 días y hospitalaria en pacientes críticos quirúrgicos con shock séptico refractario.

Pacientes y métodos. Realizamos un estudio retrospectivo antes-después en pacientes con shock séptico refractario. Según el protocolo local, se inicia tratamiento con hidrocortisona en situación de shock séptico refractario. En enero de 2017 se cambió el protocolo y se incluyó vitamina C y tiamina. Los pacientes que fueron ingresados en 2015-2016 y 2017-2018 se incluyeron en el grupo control y tratamiento, respectivamente. Los objetivos primarios fueron la mortalidad a los 28 días y hospitalaria. Los objetivos secundarios fueron la mortalidad en UCI, la duración de estancia en UCI y hospitalaria, la duración del tratamiento vasopresor y de la ventilación mecánica, el uso de técnicas de reemplazo renal (TRR), y la modificación en la procalcitonina sérica y la puntuación SOFA durante las primeras 72h.

Resultados. Se incluyeron un total de 120 pacientes (58 en el grupo tratamiento y 62 en el grupo control). El test Log-rank en las curvas de Kaplan-Meier mostró mortalidad a los 28 días y hospitalaria más baja a lo largo del tiempo en el grupo tratamiento (p=0,021 and p=0,035, respectivamente) pero no alcanzó significación estadística en la mortalidad en UCI a lo largo del tiempo (p=0,100). La necesidad de TRR fue menos frecuente en el grupo tratamiento (17,2% vs. 37,1%, p=0,024). No hubo diferencias en otros resultados secundarios.

Conclusiones. La administración de vitamina C y tiamina intravenosa en pacientes quirúrgicos con shock séptico refractario podría estar asociada a una menor mortalidad a los 28 días y hospitalaria. Se necesitan más estudios prospectivos en pacientes con shock séptico refractario.

Palabras clave: shock séptico; vitamina C; tiamina; mortalidad; vasopresor

INTRODUCTION

Sepsis is defined as a potentially fatal organ dysfunction produced by a dysregulated host response to infection [1]. The incidence of sepsis has raised, presumably due to the growing aging of the population, provided that several studies have evidenced a relationship between age and incidence of sepsis and a higher number of people with disease comorbidities [2]. Several studies have showed a lower mortality associated to sepsis over the years [3-5]. However, the total number of patients that die as a result of sepsis is growing, resulting in more than 5 million deaths world widely every year. These numbers make sepsis a major public health concern [6]. New therapeutic interventions for sepsis have been investigated over the last decades with uncertain benefits [7]. Therefore, there is an imperative need for new interventions to restrict sepsis-induced tissue damage and organ dysfunction.

Vitamin C regulates inflammation through antioxidant activity and is a primary co-factor for the synthesis of endogenous adrenaline, cortisol, and vasopressin [8]. During sepsis, vitamin C may prevent neutrophil-induced lipid oxidation and protect against endothelial barrier loss [9]. In a recent study, vitamin C administration ameliorated peripheral tissue perfusion and microvascular reactivity [10]. Thiamine is a crucial co-factor in glucose metabolism, adenosine triphosphate generation, and nicotinamide adenine dinucleotide phosphate production, as well as glutathione cycling, an important antioxidant pathway [11]. Moreover, thiamine may reduce the risk of renal oxalate crystallization [12]. Even though a recent retrospective study revealed that the combination of vitamin C, hydrocortisone, and thiamine improved survival in patients with sepsis [13], several randomized trials of vitamin C alone or in combination with hydrocortisone and thiamine have been performed without showing association with a significantly improved outcome [14-17]. The use of corticosteroids has been shown to reverse septic shock [18,19], but only in one trial it was possible to control hydrocortisone administration [15]. Vitamin C administration is not well studied in refractory septic shock.

This retrospective before-and-after study aimed to evaluate whether early vitamin C and thiamine administration was associated with lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock.

PATIENTS AND METHODS

Study design and participants. We performed a retrospective before-and-after study on patients with refractory septic shock admitted to the Surgical Critical Care Unit (SCCU) of the University Hospital La Paz (Madrid, Spain) between January 2015 and December 2018. The study was approved by the institutional review board (HULP PI 3738) and by the Spanish Medical Agency. The research was consistent with the principles of the declaration of Helsinki. The study was performed in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement [20]. Septic shock was defined according to sepsis-3 definition as sepsis, requirement of vasopressor therapy to maintain main arterial pressure (MAP) ≥65 mm Hg and serum lactate level >2 mmol/L, despite adequate fluid resuscitation [1]. Septic shock was considered refractory if norepinephrine dose >0.5 μg/Kg/min was required (expressed as norepinephrine tartrate), or equivalent dose of another drug, as previously defined [21]. Patients were included in the study if they had a refractory septic shock with adequate source control during the inclusion period. They were excluded if they were younger than 18 years; they were pregnant or breastfeeding; they had a "do not resuscitate" order in case of cardiac arrest; Simplified Acute Physiology Score (SAPS II) was > 65 at admission, or they had chemotherapy or bone marrow transplant-induced neutropenia. According to SCCU protocols, all patients received standard treatment according to Surviving Sepsis Campaign Guidelines, including broad spectrum-antibiotics initiation that was then de-escalated according to microbiologic data and clinical evolution and vasopressors to maintain a main arterial pressure ≥65 mmHg. Initial resuscitation was performed with 30 ml/kg of IV crystalloid fluid, and we guided additional resuscitation by reassessment of hemodynamic status. According to local protocol, balanced crystalloids were employed. Renal replacement therapies (RRT) were initiated in patients with acute kidney injury (AKI) and an absolute indication (refractory hyperkalemia, refractory acidemia and metabolic acidosis, refractory pulmonary edema due to fluid overload, and complications attributable to uremia). Continuous RRT were employed. Norepinephrine was the vasopressor of the first choice. Vasopressin was not available at our institution [22]. According to local protocol, hydrocortisone 200mg every 24h in continuous infusion is initiated in case of refractory septic shock. In January 2017, the protocol changed and vitamin C 1.5 g every 6h for 4 days or until ICU discharge and thiamine 200 mg every 12 h for 4 days or until ICU discharge were included in case of refractory septic shock. Patients who were admitted to our SCCU between January 2015 and December 2016 and met inclusion criteria were included in the control group, and patients admitted between January 2017 and December 2018 and met inclusion criteria were included in the treatment group. Clinical and demographic data, including age, sex, comorbidities, site of infection, use and duration of vasopressors, duration of mechanical ventilation, occurrence of acute kidney injury (AKI) according to KDIGO guidelines, use of renal replacement therapies (RRT); and laboratory data, including procalcitonin (PCT), serum lactate and serum creatinine at treatment initiation and PCT after 72h were recorded. The Simplified Acute Physiology Score II (SAPS II) at Intensive Care Unit (ICU) admission and the Sequential Organ Failure Assessment (SOFA) at treatment initiation and after 72h were calculated to assess the severity of the illness. Length of ICU and hospital stay (LOS) and ICU, 28-day and in-hospital mortality were recorded too.

Objectives. The primary objective of our study was to assess the association between the use of vitamin C and thiamine with 28-day and in-hospital mortality in refractory septic shock. The secondary objective was to assess the association of

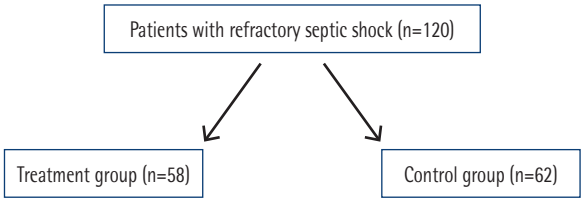

Figure 1 | **Flow chart of included patients.**

the use of vitamin C and thiamine with ICU mortality, ICU and hospital LOS, duration of vasopressors and mechanical ventilation, use of RRT, and the modification in serum PCT and SOFA score during the first 72 h (DPCT 72h and DSOFA 72h respectively).

Statistical analyses. The categorical variables were described by frequency (%), and quantitative variables by mean (SD) or medians and interquartile range, as appropriate. Univariate analysis by Fisher exact or $\chi 2$ test for categorical variables and the Student's T-Test or Mann-Whitney U test for quantitative variables was performed to compare data between the treatment and control groups. Kaplan–Meier survival curves were constructed to compare mortality within 28 days, in hospital and ICU. Cox regression multivariable models (step-wise procedure) were performed using 28-day and in-hospital mortality as dependent variables, and those with clinical-epidemiological relevance and/or showing differences in the univariate analysis as independent variables. The limit of 5 to 10 events (or nonevents, whichever is less) per introduced variable was not exceeded. Data were analyzed with SAS 9.3 statistical software (SAS Institute Inc, Cary, NC). We admitted as statistically significant those comparisons whose p-value was below 0.05.

RESULTS

A total of 120 patients with an average age of 67.6 ±14.2 years were included in the study. A total of 58 patients (48.3%) were included in the treatment group and 62 (51.7%) in the control group (Figure 1). In table 1 we present baseline characteristics of patients according to treatment group. Arterial hypertension (AHTN) was the most frequent comorbidity (n=79, 65.8%). Patients in the treatment group had a history of cardiac failure less frequently (6.9% vs. 22.6%, p=0.021). There were no differences between groups for other variables. Mean SAPS II at ICU admission was 50.7 ±17.6, without differences between groups. In most patients, the source of infection was abdominal, presenting with complicated intra-abdominal infection (CIAI) (80.0%). Patients with CIAI, complicated urinary tract infections (CUTI), skin and soft tissue infections, vascular graft infections, and mediastinitis underwent emergency surgery for source control. Regarding the surgical site in CIAI, the colon was the most frequent (31 patients), followed by biliary tract (22 patients), small bowel (21 patients), gastroduodenal tract (13 patients) and others (6 patients), without differences between groups (p=0.813).

The 28-day and in-hospital mortality rate was 31.7% and 39.2%, respectively. The 28-day mortality was lower in treatment group (22.4 %vs. 40.3%, p=0.049) but there were no differences in hospital mortality (31.0% vs. 46.8%, p=0.094). Regarding secondary end points, ICU mortality was lower in the treatment group (17.2% vs. 37.1%, p=0.024) and the need for RRT was less frequent (17.2% vs. 37.1%, p=0.024). There were no differences between groups in other secondary outcomes (Table 2).

Log-rank test in Kaplan-Meier curves showed lower 28-day and in-hospital mortality over time in the treatment group (p=0.021 and p=0.035, respectively). Log-rank test did not reach statistical significance in ICU mortality over time (p=0.100). The Kaplan-Meier curves for 28-day survival are presented in Figure 2.

In multivariable cox regression analysis, only age and DSOFA 72h were independent predictors of 28-day mortality (OR=1.043, 95% CI 1.012-1.076, p=0.006; and OR=0.861, 95% CI 0.775-0-957, p=0.006, respectively), after adjusting for group, coronary arterial disease (CAD) and body mass index (showing differences in the univariate analysis). Age and DSOFA 72h were also independent predictors of hospital mortality, after adjusting for the same variables (OR=1.044, 95% CI 1.015-1.073, p=0.002; and OR=0.875, 95% CI 0.799-0-959, p=0.004, respectively).

DISCUSSION

The main finding of this analysis suggests that the administration of vitamin C and thiamine may be associated with lower 28-day and in-hospital mortality in surgical critically ill patients with refractory septic shock. Although patients in the treatment group had a history of cardiac failure less frequently, this variable was not associated to mortality, so this finding probably does not affect results.

Marik et al found in another retrospective study a reduction in hospital mortality with hydrocortisone, vitamin C, and thiamine administration in patients with severe sepsis and septic shock, with similar mortality and severity in control group (40.4% and SOFA at admission 8.7±3.7) [13]. Although several randomized trials have not shown significantly improved outcomes with the use of vitamin C [14-17], the only trial that compared vitamin C, thiamine, and hydrocortisone vs. hydrocortisone was the VITAMINS randomized clinical trial [15]. In the CITRIS-ALI randomized clinical trial [14], performed on patients with sepsis and severe acute respiratory failure, authors did not find differences between groups in primary outcomes (modified SOFA score and plasma biomarkers levels), but 28-day mortality as a secondary outcome was lower in the intervention group (29.8% vs. 46.3%, p=0.03). In trials that did not find differences in 28-day or 30-day mortality, it ranged from 20.4% to 29.30% in the control group. These different results

Table 1 Baseline characteristics.

Variable	Total (n=120)	Treatment group (n=58)	Control group (n=62)	p
Age (years), mean ± SD	67.6 ± 14.2	66.1 ± 13.9	69.0 ± 14.3	0.336
Male, n (%)	69 (57.5)	31 (53.4)	38 (61.3)	0.461
Comorbidities, n (%)				
AHTN	79 (65.8)	39 (67.2)	40 (64.5)	0.848
DM	35 (29.2)	18 (31.0)	17 (27.4)	0.692
Cardiac failure	18 (15.0)	4 (6.9)	14 (22.6)	0.021
CAD	19 (15.8)	6 (10.3)	13 (21.0)	0.137
Stroke	6 (5.0)	2 (3.4)	4 (6.5)	0.681
Chronic renal failure	18 (15.0)	6 (10.3)	12 (19.4)	0.206
SAPS II, mean ± SD	50.7 ± 17.6	51.3 ± 14.9	50.10 ± 20.0	0.372
SOFA, mean ± SD	8.1 ± 3.3	7.8 ± 3.5	8.3 ± 3.0	0.410
Site of infection, n (%)				
CIAI	96 (80.0)	44 (75.9)	52 (83.9)	No p value
CUTI	12 (10.0)	6 (10.3)	6 (9.7)	
Skin and soft tissue	6 (5)	5 (8.6)	1 (1.6)	
Vascular graft	1 (0.8)	1 (1.7)	0 (0.0)	
Mediastinitis	1 (0.8)	0 (0.0)	1 (1.6)	
Catheter-related	1 (0.8)	0 (0.0)	1 (1.6)	
CAP	1 (0.8)	1 (1.7)	0 (0.0)	
Unknown	2 (1.6)	1 (1.7)	1 (1.6)	
PCT (ng/mL), mean ± SD	29.53 ± 58.76	26.69 ± 51.32	32.22 ± 65.37	0.945
Lactate (mmol/l), mean ± SD	3.66 ± 2.52	3.64 ± 2.56	3.68 ± 2.50	0.765
Creatinine (mg/dl), mean ± SD	1.77 ± 1.04	1.76 ± 1.03	1.79 ± 1.06	0.811

AHTN: arterial hypertension; DM: diabetes mellitus; CAD: coronary arterial disease; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; CIAI: complicated intra-abdominal infection; CUTI: complicated urinary trasct infection; CAP: Community-Acquired Pneumonia; PCT: procalcitonin.

might be due to the inclusion of more severe patients in the CITRIS-ALI trial and in our study, as we included only patients with refractory septic shock. Furthermore, Shin et al performed a before-and-after multicenter analysis that included 1,144 patients with septic shock that found that treatment with early vitamin C and thiamine was associated with lower in-hospital mortality rates in the subgroup of patients with SOFA scores>10 [23]. All these results are consistent with a nationwide cohort study performed by Jung et al, that reported that vitamin C administration was associated with a lower hospital and 90-day mortality in patients with older age, a larger amount of comorbidities, septic shock, and under mechanical ventilation [24]. However, in a recent randomized, placebo-controlled trial performed in patients with sepsis receiving vasopressor therapy, authors found a higher risk of death or organ dysfunction at 28 days in patients who received vitamin C [25].

No differences were found in the duration of vasopressors between groups, similarly to recent randomized controlled trials [15,17,26]. Rosengrave et al, in a pilot randomized controlled trial, observed no differences in vasopressors duration and dose [26]. In contrast, Mahomoodpoor et al demonstrated a reduction in the duration of mechanical ventilation and vasopressors in critically ill patients with severe pneumonia with the use of vitamin C [27]. They also found a reduction in PCT levels. Only a small proportion of their patients received corticosteroids. However, in our study all patients in both groups received corticosteroids. The possible effect of corticosteroid use on this result is unclear. A metaanalysis performed by Hemilä et al also reported a reduction in the duration of mechanical ventilation with the use of vitamin C [28].

We found a lower frequent need for RRT in the treatment

Table 2 Outcome by study group.

Variable	Total (n=120)	Treatment group (n=58)	Control group (n=62)	p
28-day mortality, n (%)	38 (31.7)	13 (22.4)	25 (40.3)	0.049
Hospital mortality, n (%)	47 (39.2)	18 (31.0)	29 (46.8)	0.094
ICU mortality, n (%)	33 (27.5)	10 (17.2)	23 (37.1)	0.024
ICU LOS (d), mean ± SD	10.7 ± 12.3	10.2 ± 9.2	11.3 ± 14.7	0.617
Hospital LOS(d), mean ± SD	31.1 ± 36.7	37.0 ± 44.4	25.7 ± 27.1	0.060
Duration of MV (h), mean ± SD	115.0 ± 268.9	76.8 ± 151.3	149.4 ± 339.8	0.111
Duration of vasopressors (h), mean ± SD	89.4 ± 113.0	86.1 ± 114.1	92.4 ± 112.9	0.940
RRT, n (%)	53 (44.2)	20 (34.5)	33 (53.2)	0.045
DSOFA 72h	2.7 ± 3.3	2.8 ± 3.1	2.5 ± 3.5	0.656
DPCT 72h (ng/mL), mean ± SD	17.7 ± 39.0	16.6 ± 38.4	18.8 ± 39.9	0.592

ICU: Intensive Care Unit; LOS: length of stay; MV: mechanical ventilation; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment; PCT: procalcitonin.

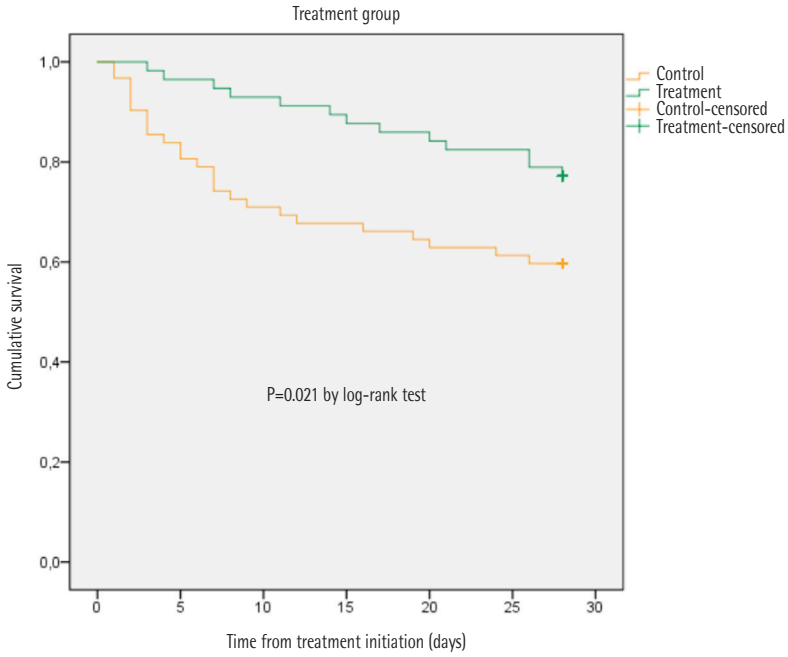

Figure 2 Kaplan-Meier curves for 28-day survival in treatment and control groups.

group as Marik et al [13]. Randomized trials that have studied kidney replacement-therapy-free days have not found any differences between groups, although the incidence of severe AKI with the need for RRT was very low [15,17]. The high frequency of RRT need in our patients (44.2%) due to severe AKI may justify this result. In 2016, during the study period, the AKIKI trial was published. Authors found no significant difference in mortality between an early and a delayed approach for the initiation of RRT [29]. As we have previously declared, according to our local protocol, in our study continuous RRT were initiated in the presence of AKI and an absolute indication, therefore our usual clinical practice did not change between 2015 and 2018.

The effect of vitamin C on underlying sepsis-induced biological anomalies may account for this difference in 28-day mortality despite the fact that we did not find any difference in terms of duration of vasopressors, duration of mechanical ventilation, and organ failure assessed by SOFA score. Furthermore, thiamine is a crucial co-factor in several metabolic pathways, and low levels may be correlated with worse outcomes [30]. Early death in the control group would require further evaluation. Furthermore, lower mortality in treatment group could explain the trend to longer LOS in this group

The absence of steady benefits in preceding trials of vitamin C in sepsis may also be attributable to inadequate dosage. For instance, some patients in the ACTS trial, with negative results, received only 1 dose of the study drug [16], and patients included in the treatment group of the CITRIS-ALI trial, that found lower 28-day mortality in the treatment group, received a higher dose of vitamin C (50 mg/kg every 6 hours) [14].

A recently published systematic review concluded that evidence from randomized controlled trials does not establish a survival benefit for vitamin C in severe infections [31]. Possibly certain phenotypes of patients, not included in randomized trials, as patients with refractory septic shock, may benefit from this treatment. Further studies are needed to elucidate the role of precision medicine in this context.

Strengths and limitations. To our knowledge, this is the first study that analyzes the association between the treatment with vitamin C and thiamine and outcomes in patients with severe refractory septic shock. Another strength is the homogeneity of included patients, given that in 80% of patients the source of infection was abdominal.

On the other hand, this study has several limitations. First, the retrospective nature of the analysis and the before-and-after design may predispose to unmeasured confounders. Besides, the non-randomized design makes it impossible to determine the causality of the association between treatment and outcomes; additionally, there are differences between groups in one comorbidity. Third, the study was performed in one tertiary academic institution with limited sample size, so the ability to generalize these results in other settings is limited. Fourth, we have no data about vasopressors total dose. Fifth, the study may be underpowered due to the limited sample size.

Conclusions. Intravenous vitamin C and thiamine administration in surgical patients with refractory septic shock may be associated with a lower 28-day and in-hospital mortality. Further prospective studies are needed to clarify the impact of vitamin C and thiamine administration in refractory septic shock.

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Demographic, clinical and microbiological characteristics of the first 30 human monkeypox confirmed cases attended in a tertiary hospital in Madrid (Spain), during the May-June 2022 international outbreak

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ABSTRACT

The present outbreak of Human Monkeypox (HMPX) that has begun in May 2022 and has spread across all continents in less than two months has qualitative and quantitative characteristics that make it different from the pattern of human disease previously caused by this virus. It has spread with enormous ease, affects almost exclusively adults, behaves as a sexually transmitted disease and focuses on very specific groups and transmission conditions. The high incidence in the city of Madrid in males that have sex with males (MSM) has allowed us to observe and report the experience with the first 30 cases diagnosed in our institution. Patients presented with febrile symptoms, genital and paragenital skin lesions reminiscent of smallpox, but less extensive and severe. The disease may also cause proctitis, pharyngitis and perioral lesions. The PCR test for diagnostic confirmation has been shown to be very sensitive and effective, not only in skin lesions but also in blood and other fluids such as pharyngeal, rectal exudates and blood. A very high proportion of patients with HMPX also have other sexually transmitted diseases that must be actively detected in this context. The spontaneous evolution of our patients has been good and hospitalization has been practically unnecessary. Transmission to non-sexual cohabitants and health personnel has been nonexistent and the lesions have disappeared in less than 30 days without leaving sequelae and no need for specific antiviral treatment.

Keywords: Monkeypox, Human Monkeypox, Sexually transmitted infections , outbreak

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Características demográficas, clínicas y microbiológicas de los primeros 30 casos humanos confirmados de viruela del mono atendidos en un hospital terciario de Madrid (España), durante el brote internacional de mayo-junio de 2022

RESUMEN

El actual brote de la enfermedad por el virus de la viruela del mono humana (HMPX), que ha comenzado en mayo de 2022 y se ha extendido por todos los continentes en menos de dos meses, tiene unas características cualitativas y cuantitativas que lo diferencian del patrón de enfermedad humana causado anteriormente por este virus. Se ha extendido con enorme facilidad, afecta casi exclusivamente a adultos, se comporta como una enfermedad de transmisión sexual y se centra en grupos y condiciones de transmisión muy específicas. La alta incidencia en la ciudad de Madrid en varones que tienen sexo con varones (HSH) nos ha permitido observar y comunicar la experiencia con los primeros 30 casos diagnosticados en nuestra institución. Los pacientes se presentaron con síntomas febriles, lesiones cutáneas genitales y paragenitales que recuerdan a la viruela, pero menos extensas y graves. La enfermedad también puede causar proctitis, faringitis y lesiones periorales. La prueba PCR para la confirmación del diagnóstico ha demostrado ser muy sensible y eficaz, no sólo en las lesiones cutáneas sino también en la sangre y otros fluidos como los exudados faríngeos y rectales y la sangre. Una proporción muy elevada de pacientes con HMPX presentan también otras enfermedades de transmisión sexual que deben ser detectadas activamente en este contexto. La evolución espontánea de nuestros pacientes ha sido buena y la hospitalización ha sido prácticamente innecesaria. La transmisión a convivientes no sexuales y al personal sanitario ha sido inexistente y las lesiones han desaparecido en menos de 30 días sin dejar secuelas y sin necesidad de tratamiento antiviral específico.

Palabras clave: Virus de la viruela del mono, Viruela del mono humana, Enfermedades de transmisión sexual, Brotes

INTRODUCTION

Monkeypox is an Orthopoxvirus discovered in Cynolmolgus monkeys in Denmark [1]. It mainly affects rodents and monkeys and humans have traditionally been considered as occasional hosts [2]. Since the first human cases of Human Monkeypox (HMPX) were reported [3], this zoonosis has been largely confined to West and Central African countries, where it has been shown to affect animals and humans in the form of small outbreaks. Most of the documented endemic cases of this zoonosis have occurred in the Democratic Republic of Congo (DRC) [4], where HMPX has produced a disease presentation similar to that of eradicated smallpox [5], except for lesser severity and the almost constant presence of enlarged regional lymph nodes.

Outside Africa, the only historically reported cases of HMPX were a multi-state outbreak of 47 cases in the USA in 2003 linked to rodents imported from Ghana [6]. Since then, a trickle of imported cases has started to be reported in non-African countries from four non-endemic countries (Israel, Singapore, USA and UK) [7-13].

However, as of May 2022, a large international outbreak of HMPX has been declared in non-endemic countries as a result of human-to-human transmission. In just over a few months, the disease has spread to all continents with more than 77 000 cases in 109 different countries [14]. Monkeypox now affects patients with no history of travel to Africa or contact with African patients, and presents almost exclusively as a sexually transmitted disease in Men Who Have Sex with Men (MSM) [15].

Spain is one of the nations with the most reported patients in this outbreak (>7,400 cases) and the community of Madrid has the highest number of episodes in Spain (>2,500 cases) [16]. For this reason, we report our experience with the first 30 cases of HMPX diagnosed and followed up in a single hospital centre in Madrid.

METHODS

Our center is a 1,200-bed university and referral hospital serving a population of about 350,000 inhabitants in the city of Madrid (Spain). The Division of Clinical Microbiology and Infectious Diseases evaluated the suspected cases of HMPX that arrived at our center during the study period; between May 19 and June 7, 2022.

The diagnosis of HMPX was suspected in patients with mucocutaneous lesions suggestive of the disease but also in patients without mucocutaneous lesions who had unprotected sex and presented with other clinical manifestations including fever, enlarged lymph nodes, proctitis or pharyngitis. In all suspected cases, a blood sample and at least one mucocutaneous lesion (when present) were examined with a polymerase chain reaction (PCR) test against monkeypox virus (MPXV). After a DNA extraction protocol of the sample with EMAG®, we used BIO-RAD® C1000™ Thermal Cycler to run a commercial PCR test from Roche® (LightMix® Modular Monkeypox Virus) in which a 106 bp fragment of the J2L/J2R gene from the monkeypox virus is amplified with specific primers and detected with a HEX labeled hydrolysis probe.

Patients also had a systematic detection of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). In all cases a screening test for syphilis (treponemal test) was performed. In patients with suspected proctitis or pharyngitis we obtained, respectively, a rectal or pharyngeal exudate, to rule out both MPXV and other sexually transmitted diseases (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and herpes simplex virus).

A confirmed case was defined as a suspected case with a positive PCR for MPXV in one or more clinical samples.

As for follow-up, all confirmed positive patients were re-evaluated between days 3 and 5 after consulting for the first time, and at day +30. In this first reevaluation, we collected a series of clinical, epidemiological and microbiological variables using a modified checklist from the one proposed by the Ministry of Health of Spain for the HPMX case declaration. We paid special attention to the oro-ano-genital location of the mucocutaneous manifestations and the date of onset of the fever in relation to rash. A contact study was also carried out in symptomatic cohabitants and the usual sexual partner. At day+30 we evaluated the clinical course, the natural evolution of the mucocutaneous lesions and the occurrence of medical complications.

Ethical approval was obtained from the Investigation Ethics Committee of the Gregorio Marañón University and Referral Hospital on the 13th July 2022.

RESULTS

During the study period, 46 patients were considered suspicious and were asked for one or more MPXV PCR tests. Of these, 30 out of 46 (65%) were confirmed to be infected with MPXV. Of the patients who were negative, an alternative diagnosis was confirmed in our laboratory in 6 of the 16 HMPX-negative cases, and they were finally diagnosed with latent syphilis (1 patient), secondary syphilis (1 patient), VHS-1 primo-infection (1 patient), VHS-1 reactivation (1 patient), varicella (1 patient) and zoster (1 patient).

Demographical characteristics. Demographic characteristics of the patients are summarized in table 1. The mean age of our patients was 33 years and all of them were less than 50 years old. None of them had received the smallpox vaccine. There were no patients from or originating from African countries. Forty-three percent were Spanish Caucasians, 47% were Latin Americans and 10% were of other origin. None of these patients had a history of travel to Central Africa in the previous 3 months.

All of our patients with confirmed HMPX infection were men who have sex with men (MSM) with a history of unprotected sex in the 4 weeks prior to clinical onset. Comorbidi-

Table 1 Demographical characteristics of the first 30 HMPX confirmed cases attended in a tertiary hospital in Madrid during the May-June 2022 international outbreak.

Age, median (IQR)	32,73+/-6,33
Country of birth	
Spain	13/30 (43%)
Other European countries	1/30 (3%)
Latinamerican	14/30 (47%)
Syrian	2/30 (7%)
MSM	30/30 (100%)
Unprotected sex	30/30 (100%)
Trip to Central Africa	0/30 (0%)
Coinfections	
HIV infection	14/30 (47%)
Newly diagnosed HIV	0/14 (0%)
Known HIV infection	14/14 (100%)
HIV infection >200 CD4	14/14 (100%)
Patients HIV (-) on PrEP	8/16 (50%)
Syphilis	4/30 (13%)
Primary Syphilis	3/4 (75%)
Syphilis of unknown duration	1/4 (25%)
HBV	0/30 (0%)
HCV	1/30 (3%)
Smallpox vaccine	0 / 30 (0%)

Table 2 Clinical characteristics of the first 30 HMPX confirmed cases attended in a tertiary hospital in Madrid during the May-June 2022 outbreak.

Fever	23/30 (77%)
Before (mucocutaneous lesions)	6/23 (26%)
At the same time (of mucocutaneous lesion)	5/23 (22%)
After (mucocutaneous lesions)	12/23 (52%)
Lymph node enlargement	
Inguinal	18/30 (60%)
Cervical	10/30 (30%)
Axillary	3/30 (10%)
Mucocutaneous lesions:	29/30 (100%)
Primary lesions location:	
External genitalia: penis, scrotum and pubic area	16/30 (53%)
Perianal and intergluteal fold	10/30 (33%)
Perioral, oral and pharynx	10/30 (33%)
Extension to other parts of the body:	
Soles of the feet	6/30 (20%)
Palms of the hands	5/30 (17%)
Legs, feet and toes	16/30 (53%)
Arms, back of hands and fingers	14/30 (47%)
Chest	6/30 (20%)
Abdomen	4/30 (13%)
Back	14/30 (47%)
Asthenia	18/30 (60%)
Sore throat	8/30 (27%)
Myalgias	12/30 (40%)
Arthralgias	7/30 (23%)
Headache	16/30 (53%)

ties included previously known HIV infection in 47% of cases. There were no other known causes of immunosuppression in the patients included in the cohort. There was active syphilis in 4 of the 30 patients (13%), which was primary in 3 of them.

Clinical characteristics. Table 2 shows the main clinical manifestations of these cases. Subclinical manifestations were frequent. Fever was present at one time or another in 23/30 (77%) of the cases, either preceding the mucocutaneous lesions or during or after their appearance. A high proportion of patients (77%) had lymph node enlargement in the inguinal, cervical or axillary regions. The frequency of arthralgias, myalgias and asthenia was high.

Mucocutaneous manifestations were frequent in almost all cases. The location of the lesions was genital, paragenital or perianal in most of the patients (figure 1). Painless vesicles and pustules on the external genitalia (penis, scrotum) or in the pubic region were the cornerstone of mucocutaneous involvement, present in 16/30 patients (53%), together with inguinal lymphadenopathies in 18/30 patients (60%). In one third of the cases the lesions were oral, perioral or pharyngeal (figure 1). Outside these areas, lesions were found in other territories in more than 50% of the patients.

We observed that 9/30 (30%) of the patients reported symptoms compatible with proctitis (rectal bleeding, mucus production from the rectum, rectal pain, sensation of fullness in the rectum, diarrhea, etc.). Sometimes proctitis was accompanied by lesions in the perianal and intergluteal area (Figure 1), as well as inguinal lymphadenopathy.

Table 3 shows the 30 cases of this series individually. The incubation period could be calculated in those patients who, in addition to remembering the day of symptom onset, clearly reported the date of the unprotected sexual intercourse.

Microbiological Characteristics:

i) MPXV diagnosis confirmation. PCR in mucocutaneous lesions confirmed the diagnosis in 28/30 cases. No viral culture was performed and therefore viability of the detected

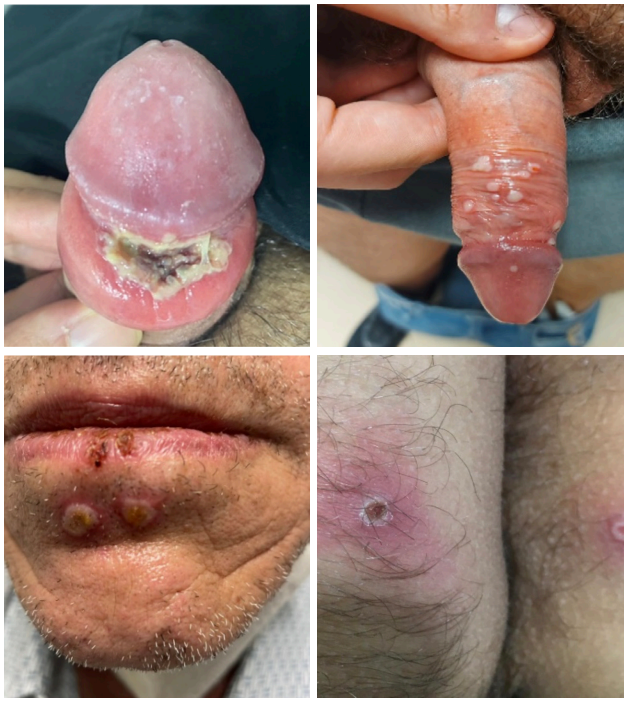

Figure 1 **A) Unique balanopreputial ulcer caused by Monkeypox; B) Multiple Monkeypox vesicles in the inner layer of foreskin; C) Monkeypox lesions in the perioral area after having oral sex; D) Monkeypox lesions in the intergluteal area in a patient with proctitis**

virus cannot be demonstrated. In the remaining 2 cases, blood PCR was positive and key to the diagnosis:

Case 16 was an HIV+ patient with fever and a very mild non-specific rash and no oro-ano-genital involvement who was studied because he was the sexual partner of a confirmed HMPX case. In this case, MPVX PCR in skin lesion was negative.

Case 27 was an HIV+ patient who presented with a sore throat and neck lymphadenopathy after oral sex. MPVX PCR in mucocutaneous lesion could not be practiced as there was no skin involvement.

Of the 28 cases confirmed positive by PCR in mucocutaneous specimens, 9 (32%) were negative by PCR in blood (figure 2). Patients with negative blood PCR did not have more extensive mucocutaneous involvement and appeared as early as the first day of symptoms (case 24) or as late as day 17 (case 5).

ii) Microbiological study of proctitis cases. Rectal exudate was obtained in 7 of the 9 patients with clinical proctitis. Of these 7 patients, MPVX-PCR was performed in 3, being positive in all of them. Results of the rest of the STDs are shown in Table 4.

Evolution and follow-up. In the first clinical reevaluation (+3-5 days), based on available microbiological results, many patients were treated for other STDs such as herpes, gonorrhea, chlamydia, *M. genitalium* or syphilis. There was only one symptomatic cohabitant, who was negative in the monkeypox study. However, three sexual partners tested positive.

One month after first medical consultation, apart from one patient hospitalized for drainage of an anal abscess, no hospitalizations were required, no other complications occurred and the patients evolved favorably while they were advised to stay at home for self-isolation with adequate pain management. We recorded no fatal outcomes. Specific antiviral treatment (tecovirimat) was not requested as, apart from being unavailable, all clinical cases progressed satisfactorily. No HMPX reinfections were detected and the skin lesions evolved favorably healing in 3-4 weeks after its appearance. The patients in whom the scabs disappeared did so without scarring.

DISCUSSION

Our study describes the clinical and epidemiological characteristics of a group of 30 patients with HMPX seen and followed consecutively in the same hospital and by the same group of researchers in Madrid in a very short period of time. All of them were men with high-risk sexual practices with other men (MSM) and in all of them MPXV infection was confirmed by PCR techniques. The infection was not limited to skin lesions and was a frequent cause of proctitis, pharyngitis and regional lymphadenopathy. The evolution was benign in all cases.

Our study provides an opportunity to analyze one of the first series of HMPX cases from the international outbreak that began in May 2022: The location of the primary lesions predominantly in the oro-ano-genital area strongly suggests that these areas play an important role in transmission of infection and were the most likely portal of viral entry. The main differential diagnosis of primary lesions in our setting was primary syphilis, genital herpes and genital zoster. Perioral lesions and oral sores, as well as sore throat without pharyngeal lesions, were probably caused by kissing or having unprotected oral sex with an HMPX-infected person. The appearance of vesicles and pustules on external genitalia or pubic region could be due to receiving oral sex or having unprotected insertive anal intercourse with an infected person. As for proctitis, in the majority of HMPX cases presenting with this syndrome, proctitis was the debut form of the disease and the main reason for clinical consultation. Secondary lesions of Monkeypox in extragenital areas appear in a scattered manner, sometimes confused with secondary syphilis, parvovirus B19 or adult varicella.

The presence of significant regional lymphadenopathy is a differential feature with episodes of classical smallpox. Diagnosis can be confirmed by PCR testing of lesions or by demonstration of MPXV in other body fluids or tissues, although in the appropriate epidemiologic setting the clinical picture is highly sugges-

Table 3 **Detailed demographical, clinical and microbiological information per case**

Confirmed cases	Sex/Age/Nationality	Incubation period	Primary lesions	Onset of fever in relation to the rash	Lymph node enlargement	PCR in blood
Case 1	cM/33/Brazilian	Unclear	O / EG	D+5	C / I	Negative (D+12)
Case 2	cM/29/Spanish	5	O	D+3	C	Positive (D+11) Ct 33
Case 3	cM/39/Spanish	Unclear	A	No fever	NO	Positive (D+6) Ct 39,2
Case 4	cM/33/Spanish	Unclear	EG	D+0	I	Positive (D+3) Ct 34
Case 5	cM/33/Spanish	Unclear	A	D+3	I	Negative (D+17)
Case 6	cM/31/Spanish	8	EG	D+2	I	Positive (D+7) Ct 37,6
Case 7	cM/32/Venezuelan	Unclear	EG	D+0	C / I	Negative (D+4)
Case 8	cM/46/Venezuelan	7	EG / A	No fever	NO	Positive (D+5) Ct 35
Case 9	cM/25/Venezuelan	10	EG	D+6	I	Positive (D+10) Ct 38
Case 10	cM/46/Venezuelan	10	EG	No fever	I	Positive (D+10) Ct 39,8
Case 11	cM//Venezuelan	Unclear	EG / A	D-2	I	Positive (D+7) Ct 34
Case 12	cM/29/Spanish	5	EG	D-3	I	Positive (D+6) Ct 35
Case 13	cM/29/Venezuelan	9	O / EG	D+3	C / I	Positive (D+4) Ct 35
Case 14	cM/26/Spanish	10	O	No fever	C	Negative (D+4)
Case 15	cM/27/Syrian	Unclear	O / EG	D+0	I	Negative (D+12)
Case 16	cM/30/Syrian	Unclear	NO	D-11	NO	Positive (D+15) Ct 36
Case 17	cM/36/Spanish	10	O	D+1	C	Positive (D+2) Ct 35,7
Case 18	cM/34/Ecuadorian	5	A	D-4	I	Negative (D+11)
Case 19	cM/41/Spanish	7	O / EG	D-1	C / I	Positive (D+1) Ct 36
Case 20	cM/40/Venezuelan	17	A	No fever	I	Positive (D+1) Ct 37
Case 21	cM/30/Venezuelan	5	EG	D+1	C / I	Positive (D+2) Ct 36
Case 22	cM/31/Venezuelan	11	EG	D+1	I	Negative (D+7)
Case 23	cM/22/Peruvian	3	O	D-1	NO	Positive (D+2) Ct 31
Case 24	cM/31/Spanish	Unclear	EG	No fever	NO	Negative (D+1)
Case 25	cM/32/Spanish	8	O	D+1	C	Positive (D+3) Ct 29
Case 26	cM/28/Honduran	Unclear	EG / A	D+1	I	Positive (D+7) Ct 29
Case 27	cM//Italian	2	NO	No fever	C	Positive (D+2) Ct 34
Case 28	cM/38/Spanish	9	A	A	NO	Positive (D+2) Ct 35
Case 29	cM/29/Cuban	2	A	D+0	NO	Negative (D+10)
Case 30	cM/37/Spanish	Unclear	A	D+1	I	Positive (D+5) Ct 36

cM, cis-male; O, Oral and Perioral; EG, External Genitalia; A, Perianal and Intergluteal fold; C, Cervical; I, Inguinal

tive of the disease. The PCR test on skin lesions proves to be very sensitive as has occurred in other series collected in our country that confirm that saliva, rectal exudate, semen, urine and blood itself, are frequently positive when obtained.

When specifically sought, a high percentage of our patients also had other sexually transmitted diseases, often undiagnosed, such as HIV infection, gonorrhea, Chlamydia infection and syphilis, corroborating data obtained in other centers in Spain and from outside Spain.

The present outbreak is peculiar in many aspects. In the quantitative side due to its dimension and rapid expansion and in the qualitative aspect due to the absence of an animal origin, its main affection in adults and its very scarce transmission outside sexual relations. The frequency of concomitant sexually transmitted diseases was very high and requires systematic screening in these patients. The evolution was benign and only one patient in our series required hospital admission for the treatment of a peri-rectal abscess.

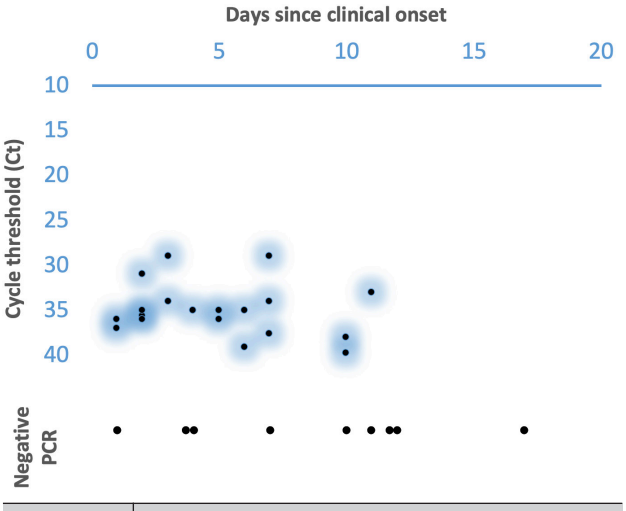

Figure 2 Results of the PCR in blood in the 28 HPMX confirmed cases by PCR in mucocutaneous lesions

Table 4 Microbiological study of rectal exudate in 9 HPMX confirmed patients with proctitis.

Number of case	Rectal swab				
	PCR HMPX	PCR TP	PCR NG	PCR CT	PCR HVS
3	NP	(-)	(-)	(-)	(-)
9	NP	NP	NP	NP	NP
11	(+)	(-)	(+)	(-)	(-)
13	NP	(-)	(-)	(-)	(-)
18	NP	NP	(-)	(-)	NP
20	NP	NP	(+)	(-)	NP
23	(+)	(-)	(-)	(-)	(-)
28	NP	NP	NP	NP	NP
30	(+)	(-)	(-)	(-)	(+)

PCR, polymerase chain reaction; HMPX, Human Monkeypox; TP, Treponema pallidum; NG, Neisseria gonorrhoeae; CT, Chlamydia trachomatis; HVS, Herpes simplex virus; (+), Positive, (-), Negative; NP, Non-practiced test

The situation of our patients did not require the use of Tecovirimat, which in any case was not available in our hospital during the first weeks of this outbreak. Something similar happened with vaccination of contacts of our patients. Imvanex type vaccines have not been available for widespread use in Spain until the second week of July 2022.

Our study has the limitation of having been collected in only one hospital but the data have been prospectively collected by a limited group of professionals with a very close follow-up of the patients.

After the experience gained with these first 30 cases, we believe it is important to rule out HMPX in any patient presenting with proctitis. In our opinion, a rectal swab should be taken for PCR of MPVX even if the patient does not appear to have mucocutaneous lesions at the time. Similarly, in patients with pharyngitis or sore throat without other clinical findings, patients should be explicitly asked whether they have recently had unprotected oral sex and, if so, consider monkeypox as a possible causative agent and take a pharyngeal swab for MPVX PCR. This may have an important implication for primary care, where we believe this infection is currently under-diagnosed.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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Tuberculosis extremadamente resistente tratada con bedaquilina

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Estimado Editor: A pesar del gran número de fármacos disponibles contra la tuberculosis (TB), todavía forma parte de las principales causas de muerte por enfermedades infecciosas [1]. Hasta la pandemia de coronavirus, la TB era la principal causa de muerte por un agente infeccioso, por encima incluso del Virus de la Inmunodeficiencia Humana (VIH) [2].

Referimos el caso de una paciente de 41 años, con nacionalidad ucraniana y residente en España desde hace 23 años. La paciente no tiene recursos económicos, no ha viajado en los últimos años y reside en un albergue municipal. Es VIH positivo sin tratamiento antirretroviral (TAR) por decisión propia, con antecedentes de episodios psicóticos en seguimiento y tratamiento con olanzapina. La paciente acude al hospital por fiebre elevada diaria (>38,5ºC). En el examen físico se observan adenopatías mediastínicas necrosadas, sugestivas de tuberculosis, por lo que se solicitaron baciloscopias seriadas, que resultaron negativas, quedando pendiente el cultivo. No se pudo realizar broncoscopia por negativa de la paciente. Tras varias negativas, finalmente se consiguió iniciar TAR con bictegravir/emtricitabina/tenofovir-alafenamida con buena tolerancia y profilaxis de *Pneumocystis jirovecii* con atovacuona 1500 mg/día por dudosa alergia a cotrimoxazol. Ante la presencia de condensación parenquimatosa en lóbulo medio y antígeno de neumococo positivo en orina se inicia tratamiento con ceftriaxona 2 g/día, secuenciando a amoxicilina/ácido clavulánico 875/125 mg/día con buena evolución clínica. Posteriormente presentó nuevamente fiebre (>39ºC) sin otra focalidad infecciosa por lo que se modificó antibioterapia a levofloxacino 500 mg/día. En la radiografía de tórax seguía observándose engrosamiento hiliar derecho, aunque con mejoría de foco de consolidación del lóbulo medio, disminución de tamaño y densidad respecto a radiografía anterior. Tras confirmarse la mejoría la paciente fue dada de alta, quedando pendiente el resultado del cultivo.

A los 10 días del alta, se informó del crecimiento de *Mycobacterium tuberculosis* en el cultivo. El servicio de Enfermedades Infecciosas se puso en contacto con la paciente para proponer ingreso. A su llegada se objetivó temperatura de 37.8ºC. Se inició tratamiento tuberculostático de primera línea con 450 mg/día de rifampicina, 75 mg/día de isoniazida, 400 mg/día de pirazinamida y 275 mg/día de etambutol. Posteriormente se añadió levofloxacino 500 mg/día tras informe del Servicio de Microbiología de resistencia a isoniazida por detección de mutación katG en el estudio genético, y se realizó broncoscopia para filiar mediante biopsia las adenopatías mediastínicas. El resultado fue positivo para *Mycobacterium tuberculosis complex* tanto en biopsia como en lavado broncoalveolar. En el estudio genético no se detectó la mutación rpoB por lo que se consideró supuestamente sensible a rifampicina. Ante la presencia de citomegalovirus en lavado broncoalveolar se solicitó carga viral en sangre, detectándose 13.900 UI/ml y tratándose con ganciclovir a 5 mg/kg/día. También recibió profilaxis a *P. jirovecii* con clotrimoxazol 400 mg/24h tras recibir pauta de desensibilización.

Tras un mes en tratamiento se confirmó, mediante estudio fenotípico, *Mycobacterium* extremadamente resistente, definido por resistencia a isoniacida, rifampicina, pirazinamida y etambutol, a moxifloxacino y a estreptomicina [3,4]. Además, el aislado era resistente a kanamicina, pirazinamida, amikacina, capreomicina y ofloxacino y sensible a P.A.S, cicloserina, etionamida y linezolid. Por todo ello se decidió modificar tratamiento: bedaquilina 400mg/día/14 días seguido de 200 mg/ 3 veces/semana, cicloserina 250 mg/día/14 días seguido de 750 mg/día, clofazimina 100mg/día, linezolid 600 mg/día y protionamida a dosis inicial de 250 mg/día.

Después de dos semanas en tratamiento la paciente se encontraba asintomática. Tras comprobar buena tolerancia y confirmar ausencia de interacción con el TAR, se dio alta. Co-

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mo efecto adverso, únicamente se objetivó hiperpigmentación cutánea en relación con clofazimina.

Al sexto mes, finalizó el tratamiento con bedaquilina. En las pruebas de imagen se informó de una clara mejoría radiológica con menor número y definición de los micromódulos pulmonares. En la actualidad, la paciente se encuentra en el mes dieciocho de tratamiento antituberculoso con cicloserina 750mg/día, clofazimina 100mg/día, linezolid 600mg/día y protionamida 500mg/12h, y presenta un buen estado general. En la siguiente consulta, al mes diecinueve, se decidirá finalizar tratamiento antituberculoso.

Presentamos el primer caso de TB tratada con bedaquilina en nuestro centro. Bedaquilina es la primera molécula autorizada que inhibe la adenosina 5'-trifosfato sintasa micobacteriana, enzima esencial en generación de energía en *M. tuberculosis* [5]. En el consenso de expertos de 2020 sobre el tratamiento de TB resistente, se recomiendan al menos cinco medicamentos en la fase intensiva, con bedaquilina como fármaco base [6].

La evidencia disponible en la práctica clínica sobre bedaquilina es reducida, sin embargo, los resultados obtenidos en nuestra paciente se asemejan a otros publicados. En un estudio retrospectivo de TB resistente a rifampicina en Sudáfrica con 19.617 pacientes, bedaquilina se asoció con reducción del riesgo de mortalidad por todas las causas (Hazard ratio 0,35, IC del 95% 0,28-0,46) [7]. En otro estudio de 197 pacientes, el 94% (186) lograron conversión del cultivo de esputo en 6 meses tras regímenes de tratamiento basados en bedaquilina [8].

En nuestra limitada experiencia, a pesar de no disponer de cultivo reciente ni de broncoscopia por imposibilidad y negativa de la paciente, se ha producido mejoría clínica y resolución radiológica. Además, no se han observado efectos adversos en relación al tratamiento con bedaquilina. En las analíticas no se objetivan alteraciones relacionados con el tratamiento, por lo que se considera seguro y bien tolerado.

La coinfección de TB y VIH continúa siendo un gran desafío en la actualidad [9]. Por ello, consideramos que casos como este en el que se consigue tratar con éxito una coinfección con un régimen basado en bedaquilina, es una opción de tratamiento esperanzadora en estos pacientes.

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CONFLICTO DE INTERESES

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Enfermedad de Whipple con presentación múltiple en paciente reumatológico. Caso y revisión de la literatura

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Paciente de 62 años que presentaba, como antecedentes de interés, insuficiencia aórtica y mitral moderada con pericarditis constrictiva, EPOC, prostatectomía radical 8 años antes por adenocarcinoma de próstata con dos recidivas, así como diarreas intermitentes desde hacía 4 años. Además, el paciente presentaba una poliartritis seronegativa (afectación bilateral de las articulaciones de muñecas, dedos y tobillos con dolor y tumefacción, así como coxalgia bilateral de predominio nocturno y derrame articular en ambas rodillas) de origen incierto desde hacía 9 años (FR, anti-CCP; ANA y HLA B27 negativos) habiendo recibido sucesivas terapias con corticoides, además de distintos inmunosupresores como metotrexato o salazopirina, y tratamientos biológicos como rituximab o baricitinib. Tras intolerancia o fracaso de los mismos, actualmente estaba siendo tratado con leflunomida (10mg/día), anakinra (100 mg/día) y prednisona (10 mg/día).

Acude por cuadro de aumento progresivo de fiebre (> 38ºC), disnea de moderados esfuerzos y diarrea acuosa. En analítica de sangre destacaban una proteína C reactiva de 190 mg/dL, 12530 leucocitos/µL, 10710 neutrófilos y 10,2 g/dL de hemoglobina (anemia ya conocida desde hace 4 años). Fue dado de alta 3 días antes por cuadro de disnea y fiebre (> 37,5ºC) asociado a derrame pleural derecho, por el que recibió en un primer momento tratamiento por vía IV con levofloxacino (500 mg/24 h) y metilprednisolona (40 mg/12 h) durante 5 días, seguido de meropenem IV (1 g/8 h durante 7 días) por nuevo pico febril. En tomografía computarizada se observó una adenopatía paratraqueal y otra infracarinal derecha ambas de 13 mm. Se intentó realizar toracocentesis guiada por ecografía visualizando mínimo derrame pleural derecho sin poder obtener débito. El estudio microbiológico realizado durante el ingreso consistente en urocultivo, hemocultivo (cuatro tandas), cultivo de esputo, quantiferon, antigenuria frente a *Streptococcus pneumoniae* y *Legionella* spp. en orina y PCR de SARS-CoV-2, virus respiratorio sincitial y virus Influenza A/B resultó negativo. También se realizó ecocardiograma transtorácico y transesofágico que confirmaron insuficiencia aórtica y mitral ya conocidas, sin estigmas de endocarditis, así como PET-TC con 18-FDG en el que no se observó aumento de actividad metabólica en las válvulas cardiacas.

Se instauró tratamiento antibiótico mediante meropenem y linezolid IV (1 g/8 h y 600 mg/12 h, respectivamente) pero, a pesar de ello, el paciente continúa con fiebre. La falta de un diagnóstico que explique un cuadro clínico de tantos años de evolución hace sospechar enfermedad de Whipple. Se realizó PCR para la detección de *Tropheryma whipplei* (RealCycler©, Progenie Molecular, Valencia, España) en muestra de sangre total en la plataforma T-Cor 8© (Tetracore, Maryland, EE. UU) con resultado positivo (valores de Ct de 33.9). También se solicitó en muestra de heces y saliva, aunque fue negativa en ambas. En la muestra de heces, además, se realizaron los paneles de PCR "Enteric bacterial" y "Enteric Viral" del sistema BD Max© (Becton Dickinson, Franklin Lakes, NJ, USA) con resultado negativo.

Para confirmar el diagnóstico se realizó gastroscopia en la que se observó un punteado blanquecino en bulbo duodenal compatible con linfangiectasias (figura 1A) y se envió muestra de biopsia para detección de *T. whipplei* mediante PCR, así como una muestra de líquido cefalorraquídeo (LCR) obtenida tras punción lumbar (líquido claro, con 300 hematíes y 3 leucocitos por µL, 51 mg/dL de glucosa y 38 mg/dL de proteínas) siendo el resultado positivo en ambas (valores de Ct de 34.9 y 31.5, respectivamente). Finalmente, tras realizar biopsia de aguja gruesa de una de las adenopatías previamente conocidas (figura 1B) se mandó muestra a anatomía patológica para estudio histológico. En ella se describieron granulomas constituidos por agrupaciones de histiocitos espumosos (figura 2A-C) y que mediante la técnica de PAS-Diastasa se tiñeron en su interior de forma gra-

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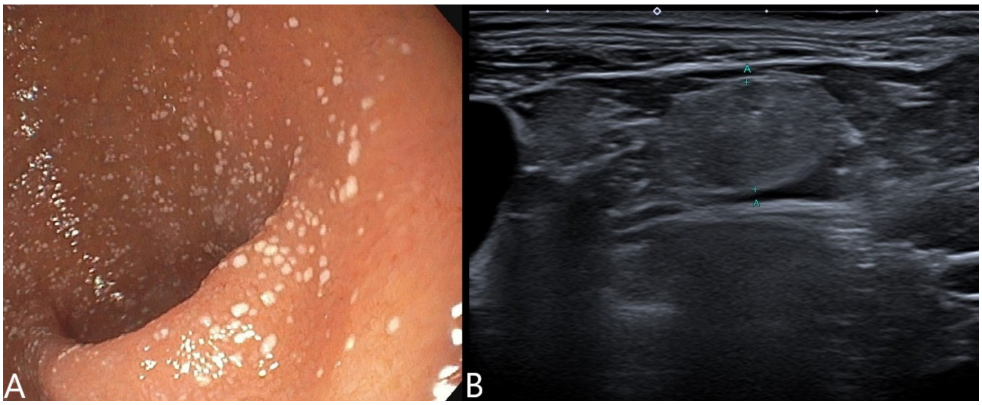

Figura 1 **A: Bulbo duodenal con punteado blanquecino sugestivo de linfangiectasias. Segunda porción duodenal con menos punteado blanquecino del mismo aspecto. Se toman biopsias para realizar PCR de *T. whipplei* que resultó también positiva.**
B: Se realiza ecografía de la región supraclavicular izquierda donde se identifican variasadenopatías de aspecto hiperecogénico de hasta 10 mm en eje corto. Con control ecográfico se realizó biopsia y enviamos muestras a anatomía patológica y al laboratorio de microbiología.

nular, compatible con EW. Además, se recuperó una muestra de biopsia duodenal realizada 3 años antes por estudio de anemia ferropénica en la que la tinción PAS-Diastasa fue negativa (figura 2D), de modo que la afectación duodenal probablemente se produjese en el transcurso de esos 3 años. La PCR de la muestra de biopsia de adenopatía resultó negativa, aunque esto pudo deberse a la poca cantidad de muestra procesada. El paciente completó 4 semanas de antibiótico IV con ceftriaxona 2 g/24 h y posteriormente comenzó con trimetoprim/sulfametoxazol 160 mg/800 mg cada 12 h, pauta que finalizará 1 año después, siendo reevaluado periódicamente (a los 6 y 12 meses) en consulta de enfermedades infecciosas mediante PCR en muestra de biopsia duodenal y sangre.

Durante las semanas posteriores, el paciente continuó con fiebre intermitente que requirió ingreso para control, y tras revisar la bibliografía fue considerado un síndrome inflamatorio de reconstitución inmune (SIRI) al coincidir con el inicio del tratamiento antibiótico. Fue tratado con dosis bajas de corticoides durante dos semanas sin otras complicaciones. Durante todo el seguimiento, el paciente no presentó en ningún momento clínica neurológica.

La enfermedad de Whipple fue descrita por primera vez en 1907, aunque no fue hasta 1952, al observar mejoría tras el tratamiento antibiótico de pacientes afectados, cuando se postuló que su causante podría ser una bacteria, *T. whipplei.* Se trata de un bacilo grampositivo intracelular de crecimiento lento, que se clasifica dentro del grupo Actinomyces y que puede estar presente en aguas residuales y materia fecal [1, 2].

Diferentes estudios muestran variabilidad en los datos de incidencia, condicionados por el número de casos en los que existe una sospecha clínica y el número de muestras en las que se solicita PCR frente a *T. whipplei.* Parece afectar principalmente a varones de raza caucásica y con edades comprendidas entre 40-75 años [3, 4]. Por otro lado, mediante screening por PCR en muestras de heces y saliva, se estima una prevalencia de portadores sanos en la población general de 1,5-7% y 0,2-1,5% respectivamente [4].

La presentación clínica de la infección causada por *T. whipplei* puede ser muy variable, aunque se puede dividir en infecciones agudas, infecciones crónicas localizadas o EW clásica. La presentación clásica consiste en pacientes con artritis/artralgias intermitentes y/o problemas digestivos crónicos como diarrea, pérdida de peso o malabsorción [5]. Los síntomas se pueden desarrollar en tres fases. Una primera fase en la que destacan fiebre y artritis/artralgias, que puede aparecer muchos años antes del diagnóstico de la enfermedad, siendo diagnosticada erróneamente como enfermedad reumática [6]. En esta primera fase es importante que los médicos sospechen una EW enmascarada siempre que los síntomas articulares de un paciente mejoren al tratar infecciones bacterianas no relacionadas [6]. Una fase intermedia donde suelen aparecer los síntomas gastrointestinales con afectación de duodeno, yeyuno e íleon, expresándose en forma de diarrea, dolor abdominal, esteatorrea, pérdida de peso o malabsorción [3]. La mayoría de los diagnósticos parecen ocurrir cuando uno o más de estos síntomas están presentes. Una fase tardía en la que se puede ver afectado cualquier otro órgano, que con mayor probabilidad serán los ojos, corazón o sistema nervioso central (SNC) [3, 5, 7]. Otros síntomas que pueden aparecer a lo largo de la evolución de la enfermedad son linfadenopatías, hiperpigmentación o derrame pleural [8]. En nuestro caso, el resultado positivo de PCR en LCR puede significar diseminación hacia el SNC, sin embargo, el paciente no presentó en ningún mo-

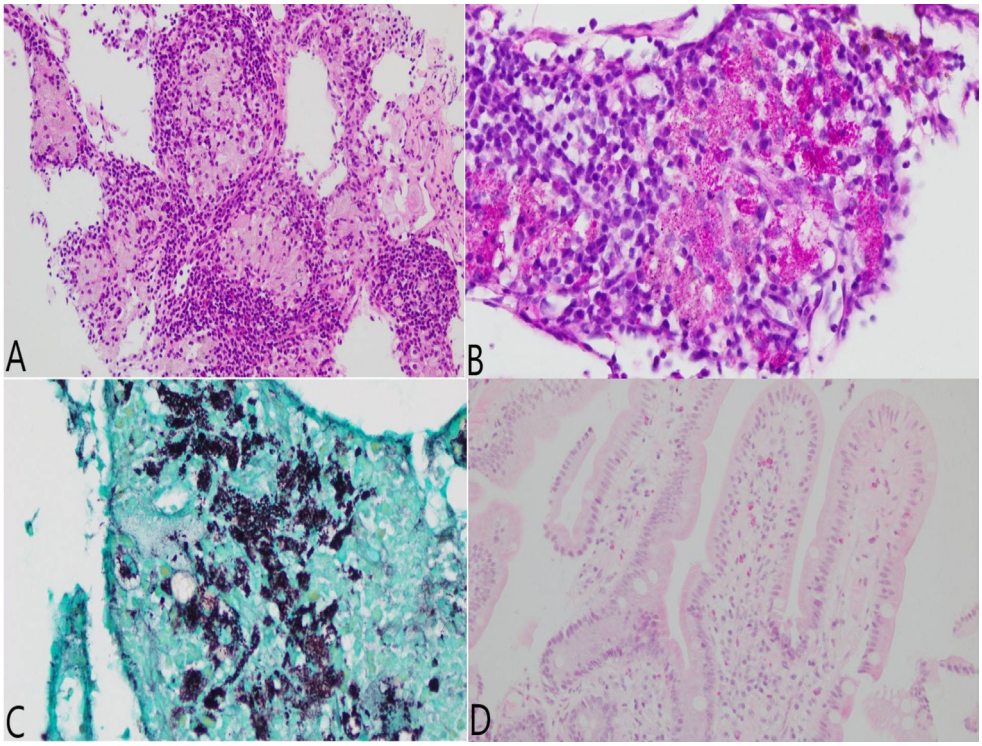

Figura 2 **A: en la tinción de H-E se observa parénquima de ganglio linfático con cambios quísticos y áreas de tejido adiposo, con formación de granulomas mal definidos, constituidos por agrupaciones de histiocitos espumosos de citoplasmas eosinófilos en áreas microvacuolado o con gránulos parduzcos. De forma entremezclada con estos granulomas se ven abundantes células plasmáticas acompañantes y linfocitos.**
B: con técnica de PAS-Diastasa vemos como el interior de los histiocitos espumosos que conforman los granulomas tiñen de forma granular, siendo PAS positivos-diastasa resistentes.
C: con técnica de Grocott también vemos como se marca de forma granular los citoplasmas de los histiocitos espumosos, con coloración pardo-oscura/negruzca. Estos hallazgos permiten diagnosticar a la biopsia como proceso granulomatoso compatible con enfemedad de Whipple.
D: en la biopsia duodenal realizada 3 años antes se observa una arquitectura de las vellosidades conservada, sin signos de atrofia, con ejes de vellosidades fibrovasculares con celularidad linfoplasmocitaria con eosinófilos, sin presencia de agrupaciones de histiocitos espumosos que pudiesen sugerir enfermedad de Whipple.

mento clínica neurológica. Por todo ello es importante prestar atención a cualquier síntoma o signo específico, y que, el antibiótico elegido para el tratamiento de la EW también presente buena difusión al SNC.

Por otro lado, a diferencia de la enfermedad clásica, la infección crónica puede afectar a órganos distintos en forma de endocarditis, encefalitis o uveítis, entre otros, sin necesidad de la presencia previa de pródromos en forma de síntomas articulares o digestivos [5,7-9]. La bacteriemia, gastroenteritis y neumonía se han visto asociadas a infección aguda [3]. En el caso que presentamos, el paciente presentaba una espondiloartropatía seronegativa tratada con diversos fármacos modificadores de la enfermedad (FAME), con intolerancias y fracaso terapéutico a lo largo de 9 años, y una PCR positiva en sangre, biopsia duodenal y LCR, así como tinción PAS positiva en muestra de adenopatía. La concurrencia de todos estos hallazgos se atribuye a la EW, aunque una evolución favorable de los síntomas articulares sin FAMEs será la que confirme el diagnóstico.

Esta enfermedad es diagnosticada frecuentemente en una

fase tardía, de modo que la sospecha clínica es muy importante. Su diagnóstico se puede establecer mediante la detección de *T. whipplei* mediante 2 tipos de técnicas diagnósticas: a) PCR específica en muestras no invasivas como sangre, saliva, heces u orina, y líquidos biológicos en función de la sintomatología que presente el paciente (LCR, líquido sinovial), o en tejidos como la biopsia duodenal y b) técnicas histológicas específicas como PAS y hematoxilina-eosina [10].

En caso de sospecha de EW clásica, si bien trabajos publicados indican que a modo de screening inicial dentro del algoritmo diagnóstico bastaría con una PCR en muestra de saliva y heces, en nuestro caso ambas PCR fueron negativas [11]. Los falsos negativos pueden ser atribuibles a la presencia de inhibidores o inóculos bajos de bacterias en la muestra. En nuestro caso, la razón por la que no se detectara *T. whipplei* por PCR en saliva o heces puede deberse a que el paciente había recibido recientemente una pauta de 7 días de meropenem (1 g/8 h). Por este motivo es recomendable incluir otras muestras no invasivas como sangre y orina. Si al menos una de ellas es positiva y la sospecha continúa siendo alta, entonces se confirmará mediante muestras invasivas que en todos los casos incluirá la biopsia duodenal, y dependiendo de los síntomas, otras muestras como adenopatías, válvula cardiaca, líquido pleural o líquido cefalorraquídeo para realización de PCR o técnicas histológicas y tinción de PAS [3]. Aunque la tinción PAS es frecuentemente utilizada, no es específica de *T. whipplei* dado que en infecciones por otras bacterias *como Mycobacterium avium intracellulare* o *Rhodococcus equi* también se pueden observar típicamente los macrófagos espumosos que contienen inclusiones PAS positivas.

El tratamiento antibiótico lleva a una mejoría rápida de la sintomatología, con desaparición de los síntomas como diarrea, dolor articular o fiebre en la primera semana [12]. La primera opción de tratamiento actualmente se basa en una pauta IV de ceftriaxona o meropenem (2 g/24 h y 1 g/8 h) durante 2 a 4 semanas para alcanzar niveles altos en LCR, seguida de una pauta prolongada de tratamiento de al menos un año con trimetoprim-sulfametoxazol oral durante 12 meses para erradicar la bacteria y evitar futuras recaídas. Este régimen de tratamiento está en discusión en los últimos años debido a que debido a que el análisis obtenido tras secuenciación completa o los estudios de sensibilidad in vitro realizados en algunas cepas sugieren una resistencia intrínseca a trimetoprim-sulfametoxazol (ausencia de dihidrofolato reductasa, así como mutaciones en el gen que codifica la dihidrofolato sintetasa) [13]. Otra de las opciones disponibles es la combinación de 200 mg/día de doxiciclina y 600 mg/día de hidroxicloroquina durante 12/18 meses, aunque se requieren más estudios prospectivos que apoyen su eficacia. Es necesario un seguimiento durante y después del tratamiento para detectar una posible recaída. Sería necesario una biopsia duodenal a los 6 meses de finalizar el tratamiento. Sin embargo, debido al carácter invasivo de esta prueba, se está estudiando la utilización de técnicas basadas en PCR para detectar *T. whipplei* en muestras no invasivas como saliva, heces u orina [14]. Finalmente, hay que tener en cuenta el posible riesgo de aparición de un SIRI en pacientes que han recibido previamente tratamiento inmunosupresor cuando comienzan la pauta antibiótica, necesitando corticoides u otros agentes inmunosupresores [15].

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Evolución temporal de las variantes de SARS-CoV-2 circulantes en el área sanitaria de Cádiz

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Desde la descripción en diciembre de 2019 del nuevo coronavirus SARS-CoV-2 se ha producido la emergencia y diseminación de múltiples variantes genéticas [1,2]. Algunas presentan un mayor riesgo para la salud pública, debido a mutaciones que aumentan su capacidad de propagación y/o la gravedad de la enfermedad que provocan, o disminuyen la eficacia de los medios diagnósticos, las vacunas o los tratamientos disponibles [3]. Las variantes con mayor implicación en salud pública han sido clasificadas en Variantes Preocupantes (VOC) y Variantes de Interés (VOI) por la Organización Mundial de la Salud ((https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Con el objetivo de conocer la epidemiología de SARS-CoV-2 en nuestra área sanitaria, analizamos la evolución temporal de las variantes circulantes durante un periodo de 16 meses.

Durante el periodo de estudio (febrero 2021 - mayo 2022) se seleccionaron aleatoriamente un máximo de 40 muestras semanales de exudado nasofaríngeo con un resultado positivo de PCR para SARS-CoV-2 para analizar la variante del virus causante de la infección mediante secuenciación masiva. Sólo se incluyó una muestra por paciente y/o brote. Las muestras siguieron el circuito de secuenciación genómica de SARS-CoV-2 establecido por la Consejería de Salud y Familia de la Junta de Andalucía. La secuenciación se llevó a cabo en el H.U. Virgen del Rocío en la plataforma MiSeq (Illumina, San Diego, CA, USA), realizándose la preparación de la librería mediante el protocolo ARTIC SARS-CoV-2 (https://artic.network) con el kit Illumina DNA Prep [4], con posterior cuantificación (Qubit DNA BR, Thermo Scientific) y normalización. El análisis de secuencias se realizó en el Área de Bioinfoirmática Clínica de la Fundación Progreso y Salud, ensamblando con la herramienta nf-core/viralrecon (https://nfco.re/viralrecon) [5], asignando los diferentes clados y anotando las mutaciones presentes con Nextclade (https://clades.nextstrain.org/) [6]. La herramienta Pangolin (https://cov-lineages.org) fue utilizada para la asignación de los linajes [7]; en aquellos genomas en los que no fue posible obtener el linaje con esta herramienta, se utilizó la aplicación impuSARS para atribuir el linaje [8].

Se analizaron 2.496 muestras, obteniéndose la variante causante en 2.380 muestras (95,4%); las 116 muestras en las que no se obtuvo la variante del virus presentaron valores de Ct superiores a 30 para los diferentes genes detectados en la PCR diagnóstica. Las variantes VOC (actuales o previas) detectadas fueron, por orden de frecuencia: Delta (747 muestras, 31,4%), Alfa (738 muestras, 31,0%), Ómicron (724 muestras, 30,4%), Gamma (9 muestras, 0,4%) y Beta (5 muestras, 0,2%). La única variante VOI detectada fue Lambda (12 muestras, 0,5%). Las 145 muestras restantes (6,1%) pertenecían a otras variantes circulantes, no clasificadas como VOC o VOI.

Con respecto a la evolución temporal de las variantes circulantes, se observaron tres periodos bien diferenciados (Figura 1). En los primeros meses del año 2021 (semanas 7 – 26) la variante Alfa fue la mayoritaria, detectándose en el 69,7 – 100% de las muestras. En la semana 27 se observó un cambio de tendencia, disminuyendo la prevalencia de la variante Alfa (47,5%), aun siendo mayoritaria, y un aumento de los casos debidos a la variante Delta (40%). A partir de la semana 28 del año 2021, la variante Delta pasó a ser la principal variante detectada, detectándose en el 60 – 100% de las muestras entre las semanas 28 y 50 del año. Desde la semana 50 del 2021 y hasta el final del periodo de estudio (mayo 2022), la variante Ómicron se convirtió en la variante mayoritaria, detectándose en el 65 – 100% de las muestras.

A pesar de que las diferentes variantes del SARS-CoV-2 difieren en sus tasas de transmisión y reinfección, así como en la gravedad de la enfermedad provocada, no existe evidencia de que respondan de forma diferencial a las medidas de Sa-

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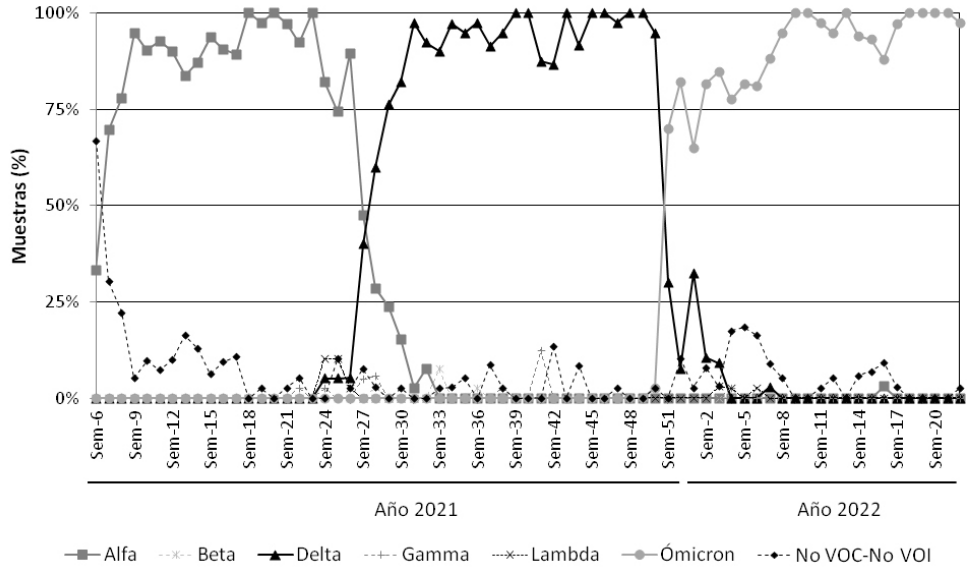

Figura 1 | **Evolución temporal de las variantes de SARS-CoV-2 circulantes durante el periodo de estudio (febrero 2021 - mayo 2022)**

lud Pública aplicadas como el distanciamiento social y uso de mascarilla, o a la mayoría de tratamientos antivirales [9]. Sin embargo, múltiples estudios han mostrado que la principal consecuencia de la emergencia de las distintas variantes es su impacto sobre la eficacia de las vacunas, observándose grandes diferencias en los niveles de anticuerpos neutralizantes generados por las diferentes vacunas utilizadas frentes a las distintas variantes de SARS-CoV-2 [10].

Estas diferencias en la respuesta a la vacunación ponen de manifiesto la necesidad de seguir realizando estudios de monitorización de las variantes circulantes, como el llevado a cabo en nuestra área sanitaria, para poder adaptar las nuevas vacunas a la situación epidemiológica actual y futura. Los estudios locales permitirán estudiar diferencias en el comportamiento del virus en diferentes áreas, pudiendo implementar las medidas más adecuadas según la situación epidemiológica local.

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CONFLICTO DE INTERESES

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Absceso cerebral por *Eikenella corrodens* como complicación de sinusitis frontal en paciente inmunocompetente

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Eikenella corrodens es un bacilo gramnegativo anaerobio facultativo, perteneciente a la familia *Neisseriaceae*, que forma parte de la microbiota normal de la cavidad oral, las vías respiratorias altas y la mucosa intestinal humana [1]. Raramente actúa como patógeno y sus infecciones suelen ser localizadas, aunque se han descrito casos invasivos en pacientes inmunodeprimidos o con otros factores de riesgo como manipulación quirúrgica de las vías aéreas, alcoholismo, drogadicción, cardiopatía y diabetes [1]. Debido a su relación con la orofaringe, una importante proporción de las infecciones están asociadas a mordedura humana [2], también se vincula con infecciones de cuello y cabeza y, en menor medida, con infecciones respiratorias o bacteriemias [3]. Pertenece al grupo HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella* y *Kingella*) relacionado con endocarditis, dentro del cual *E. corrodens* es el integrante menos frecuente.

Como agente etiológico de infecciones del sistema nervioso central (SNC) solo existen reportes anecdóticos en la literatura científica. Se presenta el caso de un paciente joven y sin factores de riesgo que desarrolló un absceso cerebral por *E. corrodens* de origen sinusal.

Paciente masculino de 18 años, sin antecedentes médico-quirúrgicos de interés ni factores de riesgos conocidos, que acudió a Urgencias del hospital por fiebre, rinorrea y cefalea persistente de predominio coronal de más de una semana de duración. Se solicitaron pruebas de imagen complementarias (TC) que evidenciaron signos de sinusitis maxilar y frontal derecha sin complicaciones endocraneales, por lo que se decidió alta hospitalaria para seguimiento ambulatorio y tratamiento con paracetamol (650 mg/8h), ciprofloxacino (500 mg/12 h, 10 días) y mometasona nasal (una vez/día, 14 días). Diez días después, tras una inicial mejoría, el paciente experimentó empeoramiento con malestar general y cefalea intensa, por lo que acudió de nuevo a Urgencias, donde tras valoración otorrinolaringológica se decidió intervenir mediante cirugía endoscópica nasosinusal realizándose una meatotomía media derecha y etmoidectomía anterior con salida de material purulento del seno maxilar y frontal, al cual se le realizó estudio microbiológico, aislándose a las 48 horas en medio de agar chocolate, unas colonias rugosas, de bordes circulares o irregulares, grisáceas, translúcidas, no hemolíticas, que erosionan el medio de cultivo y con ligero olor a lejía (Figura 1), identificadas mediante espectroscopia de masas (MALDI-TOF) como *E. corrodens*, mostrando sensibilidad, por técnica de E-test y criterios CLSI, a amoxicilina/clavulánico, ceftriaxona, meropenem, ciprofloxacino, doxiciclina y cotrimoxazol. Se inició tratamiento con cotrimoxazol (800/160mg vo/8 h), dada la estabilidad del paciente

Figura 1 **Colonias de *Eikenella corrodens* en agar chocolate a las 48 horas de incubación a 37º C en atmósfera de 5% de CO_2.**

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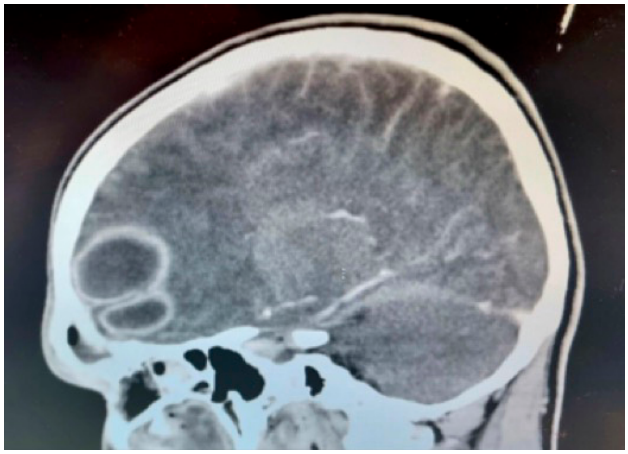

Figura 2 | **TC cerebral en corte sagital con contraste donde se observan dos LOE con realce en anillo en lóbulo frontal derecho de 35x29mm y de 26x25mm sugerentes de absceso cerebral en región frontal derecha.**

se decidió alta hospitalaria. A los cinco días, volvió a ingresar por cefalea intensa y vómitos, sin otros signos de irritación meníngea y analítica sanguínea sin parámetros de inflamación (PCR 3,7mg/L; leucocitos 11,09/mm^3). Se decide reingreso para realizar un nuevo TC evidenciándose dos lesiones ocupantes de espacio compatibles con abscesos cerebrales (Figura 2). Se decidió drenaje quirúrgico mediante abordaje externo y tratamiento empírico con meropenem (2g iv/8h), linezolid (600mg iv/12h) y dexametasona (4mg iv/6h). Se remitieron muestras para Microbiología, observándose en el examen microscópico directo bacilos gramnegativos. A las 24 horas se informó cultivo positivo para *E. corrodens*, mostrando mismo resistotipo que aislamiento previo. Los hemocultivos fueron negativos y la ecocardiografía no mostró alteraciones. Tras el informe de microbiología, se inició tratamiento dirigido con amoxicilina/clavulánico (875/125mg cada 8h, 3 semanas). El paciente mostró una evolución favorable, con ausencia de secuelas neurológicas y resolución de las imágenes radiológicas.

La patología sinusal sigue siendo un motivo de consulta frecuente, aunque sus complicaciones son poco habituales. Los abscesos cerebrales posteriores a sinusitis aguda o crónica se suelen localizar en lóbulo frontal, debido a la proximidad anatómica de los senos etmoidales frontal y posterior [4]. *Streptococcus* spp. es el agente microbiano aislado con mayor frecuencia, aunque otros patógenos pueden estar involucrados [5]. En España, un estudio retrospectivo sobre infecciones profundas causadas por *E. corrodens* no detectó cuadros en SNC, considerándose un patógeno raro a nivel de abscesos cerebrales [3]. En una búsqueda bibliográfica sistemática (base de datos: Pubmed; MeSH utilizados: *Eikenella* and *brain* or *cerebral* or *central nervous system infection*) se encontraron cuatro casos clínicos de abscesos a nivel de SNC relacionados con *E. corrodens* en los últimos 10 años, tres de los cuales estaban relacionados con patología odontológica y el cuarto secundario a endocarditis [6-9].

La causa principal de absceso cerebral es la transmisión por continuidad de un foco localizado, incluyendo otitis, mastoiditis y sinusitis [6], siendo recomendable descartar complicaciones en el sistema nervioso central en aquellas sinusitis que no presenten mejoría luego de tratamiento o presentan focalidad neurológica [4].

Desde el punto de vista antibiótico, *E. corrodens* muestra resistencia a metronidazol, cloxacilina, cefalosporinas de primera y segunda generación, macrólidos y clindamicina, los cuales no deben emplearse en caso de sospecha de infección por *Eikenella* [3]. Aunque suele mostrar alta sensibilidad a amoxicilina/clavulánico, cefalosporionas de 3ª generación, fluoroquinolonas, tetraciclinas, cotrimoxazol y carbapenémicos, deben realizarse estudios de susceptibilidad a antimicrobianos y ajustar el tratamiento, evaluándose la respuesta clínica y descartando la formación de abscesos, los cuales deben drenarse en caso de aparición [10].

A pesar de los avances en el diagnóstico y tratamiento, los abscesos a nivel de sistema nervioso central siguen presentando una elevada tasa de morbimortalidad [5] por lo que su diagnóstico y tratamiento temprano son cruciales, especialmente en los casos de patógenos inusuales como es el caso de *E. corrodens*.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses

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Carta al Director

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Absceso hepático amebiano en paciente procedente de Gambia

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Estimado Editor:

La amebiasis producida por *Entamoeba histolytica* es una parasitosis que afecta aproximadamente a 40 millones de personas en el mundo, causando 100.000 muertes al año [1]. Este parásito, cuya transmisión es vía fecal-oral, se observa con frecuencia en personas procedentes de zonas endémicas (India, África, México y América Central y del Sur) y viajeros [2]. La mayoría de las personas que se infectan por *E. histolytica* son portadores asintomáticos (90%) [3]. La colitis amebiana generalmente tiene un inicio subagudo, con síntomas que pueden variar desde diarrea leve hasta disentería severa. Algunos pacientes pueden llegar a desarrollar amebiasis extraintestinal invasiva, siendo el absceso hepático amebiano la manifestación extraintestinal más frecuente (2-5%) [4]. Hoy en día, con un tratamiento eficaz, la tasa de mortalidad de los pacientes con enfermedad no complicada es inferior al 1 %. Sin embargo, en el 5-10 % de los casos, puede complicarse con rotura del absceso, aumentando potencialmente la mortalidad. Por este motivo, hemos considerado de interés exponer este caso poco frecuente en nuestro entorno, pero a tener en cuenta en el diagnóstico diferencial del absceso hepático en este tipo de pacientes.

Varón de 17 años procedente de Gambia sin antecedentes conocidos, que tras su llegada a la isla de Tenerife comenzó con dolor abdominal de predominio epigástrico, acompañado de náuseas y vómitos, que persistió durante días irradiándose hacia hipocondrio derecho y fosa renal derecha, fiebre (39ºC) y PCR elevada (223,77mg/l). Se realizó ecografía abdominal, encontrándose hallazgos sugestivos de absceso hepático de 8x8x9 cm.

Al ingreso, el Servicio de Infecciones pautó tratamiento antibiótico intravenoso con ceftriaxona 2g/24 h y metronidazol 750mg/8h. Además del despistaje de enfermedades protocolizado para este tipo de paciente (Serologías VHB, Quantiferón), se solicitó estudio de parásitos en heces (test de concentración Miniparasep®SF (Grifols) y PCR multiplex GI-FilmArray®) y PCR de *E.histolytica* en sangre, obteniendo resultados negativos en todas las determinaciones. Por último, se remitió muestra de suero al laboratorio de referencia para el estudio de anticuerpos de *E. histolytica*.

En la ecografía de control (a los 5 días) se evidenció mejoría radiológica con disminución del tamaño del absceso (5x4,2 cm). Dado el resultado negativo de las pruebas solicitadas y, a falta del resultado del centro de referencia, se decidió realizar punción del absceso y recogida del material purulento para estudio de parásitos y cultivo (Figura 1).

Se realizó tinción tricrómica tipo Wheatley del absceso (Figura 2), observándose estructuras sugestivas pero no concluyentes de *E.histolytica*. A su vez, se realizó Panel GI-FilmArray® a pesar de no estar validado para dicha muestra, resultando positivo para *E. histolytica*. A su vez, se recibió el resultado de la serología del centro externo, siendo positivo para *E. histolytica* (IgG).

Tras 18 días ingresado, el paciente fue dado de alta.

La presentación clínica de absceso hepático generalmente ocurre dentro de las 8 a 20 semanas post-infección, aunque puede ser asintomático durante años [5]. Suele aparecer dolor en hipocondrio superior derecho, fiebre y hepatomegalia. Sólo el 10-35% de los pacientes con absceso hepático presentan síntomas gastrointestinales asociados a disentería amebiana y menos del 20% de los pacientes presentan parásitos en heces. Dado que los síntomas y signos son inespecíficos y el examen de heces puede ser negativo, suelen ser útiles las pruebas de imagen (ecografía) y las pruebas serológicas, teniendo en cuenta que, en pacientes provenientes de áreas endémicas, el valor de estas pruebas es controvertido, ya que cerca del 35% de esta población tiene anticuerpos debido a su alta prevalencia.

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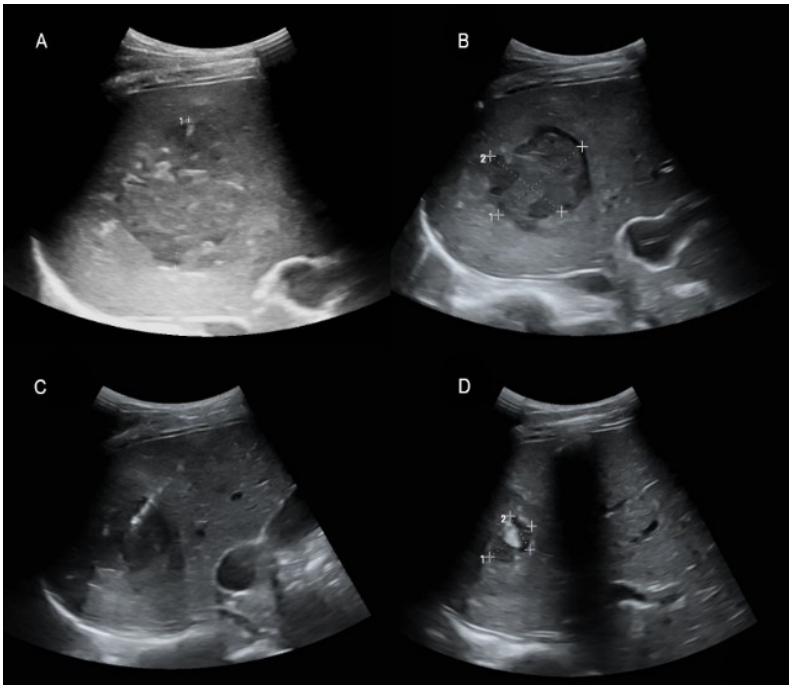

Figura 1 | **A: Imagen de ecografía con absceso hepático 8 x 8 x 9 cm. B: Disminución del tamaño de absceso. C: Punción diagnóstica. D: Imagen del absceso hepático tras punción**

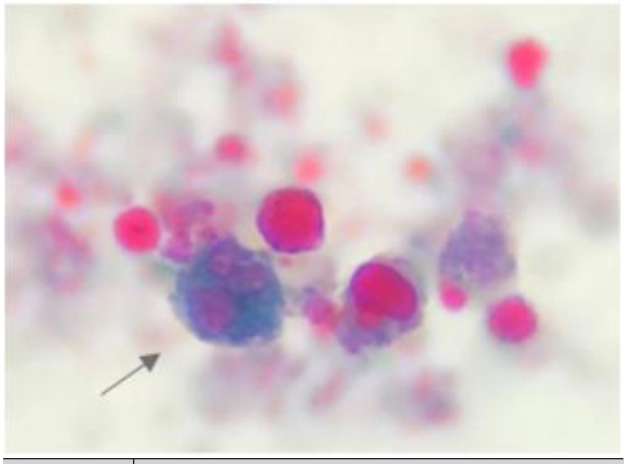

Figura 2 | **Tinción tricrómica**

El diagnóstico confirmatorio incluye la detección de *E. histolytica* del material biopsiado [6], aunque sólo se considera necesario el drenaje quirúrgico en aquellos casos resistentes al tratamiento, contraindicaciones (embarazo), riesgo de rotura del absceso o extensión pleuropulmonar [7]. Nuestro caso pone en evidencia la posibilidad de utilizar técnicas moleculares en muestras no validadas como el drenaje de absceso. El tratamiento de la amebiasis invasiva incluye un amebicida tisular (metronidazol 750 mg/8h oral o intravenoso) y un amebicida intraluminal (paramomicina 500 mg/8h oral) durante 10 días.

Creemos importante incluir esta patología en el diagnóstico diferencial de estos pacientes, dado el incremento de población migrante procedente de zonas endémicas causado por la actual crisis migratoria. En aquellos casos con sospecha de amebiasis extraintestinal, se deben utilizar con celeridad todas las herramientas diagnósticas disponibles, incluyendo técnicas moleculares en muestras para la cual todavía no están validadas.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Letter to the Editor

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Bacteremia caused by *Clostridium sporogenes* in an oncological patient

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Sir,

Clostridium sporogenes is a Gram-positive anaerobic bacillus firstly described by Metchnikoff E. in 1908 [1]. This pathogen is a member of the normal microbiota of the gastrointestinal tract, and it has been implicated in some human infections such as septic arthritis and myonecrosis [2,3]. This bacterium rarely causes bloodstream infections, which are mainly caused by *C. perfringens*. We recently observed an uncommon case of bacteremia due to *C. sporogenes* isolated in pure culture in a patient with a clinical history of cancer.

A 70-year-old man was admitted to the Emergency Department of our hospital after 2 weeks with diarrhea, vomiting, and abdominal pain. His clinical history was remarkable for a lung cancer currently in treatment with radiotherapy and chemotherapy (TAXOL + CARBOPLATINE), and for a type II diabetes mellitus. The physical exam only showed an abdominal pain without other signs. Blood analysis showed increased levels of glucose (157 mg/dL) and C-reactive protein (341.2 mg/L) and decreased levels of red cells blood count (2.83 x 10^6/mm^3). The patient was then admitted to the Oncology Department for study. Three days after admission, the patient developed fever (38.4º C) and low blood pressure (106/68 mmHg). Two sets of blood cultures were taken and sent to the microbiology laboratory, while empirical treatment was started with meropenem (1 g/12 h./i.v.). Due to the persistence of abdominal pain and the presence of rectal bleeding, an abdominal CT scan was performed appearing signs of intestinal perforation due to acute diverticulitis.

In the microbiology laboratory, samples were inoculated onto the BACTEC FX 40 (Becton Dickinson, Franklin Lakes, NY) monitorization system for culture. On day 1 of incubation, the two anaerobic bottles from two blood culture sets were positive. The samples were subcultured on aerobic or anaerobic blood agar (BD Columbia Agar with 5% Sheep Blood, Becton Dickinson, Franklin Lakes, NY). All media were incubated at 37 ºC. The AnaeroGen Compact anaerobic system (Oxoid Ltd, Wide Road, Basingstoke, England) was used. Gram staining of the blood cultures revealed abundant Gram-positive bacilli; on 24 hours of incubation, abundant colonies of these microorganisms were observed in pure culture on anaerobic blood agar alone. MALDI-TOF MS version 9 (8468 msp) (Bruker Biotyper, Billerica, MA) was employed, identifying the strain as *C. sporogenes* (score 2.35). The strain was sent to the Centre of Genomic and Oncologic Research (GENYO, Granada, Spain) for 16S rRNA gene sequence analysis using a previously reported method [4]. A fragment of 1,329 bp was obtained, yielding 99.85% similarity with the *C. botulinum* type strain Mfbjulcb5 GenBank sequence (accession number CP027776.1) and *C. sporogenes* strain CDC 1632 GenBank sequence (accession number CP013243.1). Subsequently, the sequence was compared using another database (IeBIBI IV 16s Automated ProKaryotes Phylogeny) confirming the strain as *C. sporogenes*. The 16S sequence was submitted to the GenBank (accession number: OP431824).

The E-test was used for antimicrobial susceptibility testing based on 2022 EUCAST criteria [5]. The following MIC values were obtained: benzylpenicillin (0.032 mg/L), piperacillin-tazobactam (0.064 mg/L), clindamycin (16 mg/L), meropenem (0.023 mg/L), and metronidazole (0.064 mg/L).

The patient was submitted to an abdominal surgical intervention. After 34 days hospitalized, the patient was discharged. His general condition remains good at 3 months of follow-up.

Bacteremia caused by *C. sporogenes* is an uncommon disease; until now, only 13 cases of bacteremia isolated in pure culture due to this bacterium have been published in the literature [6-11]. Table 1 shows the main characteristics of patients with bacteremia due to *C. sporogenes*.

Among species of the genus *Clostridium* that have been

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Table 1 **Main characteristics of *Clostridium sporogenes* bacteremia isolated in pure culture.**

Case [reference] (year of publication) Author	Age (years)/sex	Identification method	Underlying conditions and/or risk factors	Clinical manifestations	Treatment	Outcome
1 [10] (1991) Bodey GP	77/F	Biochemical method Gas-liquid chromatographic analysis	Colorectal cancer	Abdominal symptoms	Antibiotics	Successful
2 [10] (1991) Bodey GP	22/F	Biochemical method Gas-liquid chromatographic analysis	Sarcoma	Fever	Antibiotics	Successful
3 [10] (1991) Bodey GP	59/F	Biochemical method Gas-liquid chromatographic analysis	Breast cancer	Fever	Antibiotics	Successful
4 [10] (1991) Bodey GP	99/F	Biochemical method Gas-liquid chromatographic analysis	Genitourinary cancer	Abdominal symptoms	Antibiotics	Successful
5 [10] (1991) Bodey GP	22/M	Biochemical method Gas-liquid chromatographic analysis	Hodgkin's lymphoma	Fever	Antibiotics	Successful
6 [10] (1991) Bodey GP	70/M	Biochemical method Gas-liquid chromatographic analysis	Colorectal cancer	Abdominal symptoms	Antibiotics	Successful
7 [10] (1991) Bodey GP	58/F	Biochemical method Gas-liquid chromatographic analysis	Genitourinary cancer	Abdominal symptoms	Antibiotics	Died
8 [10] (1991) Bodey GP	45/F	Biochemical method Gas-liquid chromatographic analysis	Acute leukemia	Fever	Antibiotics	Successful
9 [6] (1996) Corbett CE	45/M	Biochemical tests	Renal transplantation	Pleuritic chest pain, fever, tachycardia, low blood pressure	Antibiotics	Died
10 [7] (2013) Shen DX	70/M	MALDI-TOF MS 16S rRNA gene sequencing	Colorectal cancer DM Abdominal surgery	Fever, tachypnea	Antibiotics	Died
11 [8] (2018) Abusnina W	66/F	NR	DM	Sepsis	Antibiotics	Died
12 [9] (2020) Vecchio MJ	81/M	NR	Abdominal surgery	Abdominal pain and distension	Antibiotics	Died
13 [11] (2020) Alataby HA	75/M	NR	Unknown	Low blood pressure, tachycardia, tachypnea, fever	Antibiotics	Successful
14 [PR] (2022) Cobo F	70/M	MALDI-TOF MS 16S rRNA gene sequencing	Lung cancer Type II DM	Diarrhea, vomiting, abdominal pain, fever	Antibiotics	Successful

M: male; F: female; PR: present report; DM: diabetes mellitus; NR: not reported

isolated in human infections, *C. sporogenes* is not frequently implicated in human infections and it is uncommon as a cause of bloodstream infections. Regarding the possible source of infection with this anaerobe, this patient showed an abdominal focus of the infection with diverticulitis. The most likely source of infection was therefore the gut, taking into account that *Clostridium* spp. form part of the normal microbiota of the gastrointestinal tract.

MALDI-TOF MS offers a rapid approach for the routine analysis of bacteria in clinical laboratories. It can be highly useful for the final identification at both genus and species level and may help to detect new species of anaerobes. Nevertheless, this technique should be applied with care, evaluating the version of the database used, the log score obtained, and the consistency of the identification. When the log score indicates high confidence but the consistency is low (as in the present case), molecular methods should be used to confirm the result and avoid misidentification.

Most *in vitro* studies suggest that *Clostridium* spp. has increased resistance to a wide range of commonly used drugs. A study showed that resistance was observed for all antimicrobials tested except for imipenem [12]. Similar results have been reported by several surveys [13-16]. However, the resistance rates are not alarmingly high but monitoring of these resistances should be performed.

Among case reports, several of them did not perform antimicrobial susceptibility testing [6,8,9,11] and one found that *C. sporogenes* isolate was susceptible to all antimicrobials tested except clindamycin [7]. In the present study, only resistance to clindamycin was detected. Susceptibility testing of these strains is essential to develop the optimal therapeutic strategy against these infections.

In conclusion, this is an uncommon case of *C. sporogenes* bacteremia isolated in pure culture and confirmed by 16S rRNA gene sequencing, indicating that this pathogen can be responsible for severe infections. This case report and recent observations of antimicrobial susceptibility among *Clostridium* spp. highlight an increased resistance to various antimicrobials and emphasize the need for antimicrobial susceptibility testing of all isolates.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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Letter to the Editor

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Soft-tissue infection due to *Mycoplasma hominis*

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Sir,

We present the case of 32-year-old black man, attended at our emergency service because of cardiac arrest produced by ventricular fibrillation. The patient was provided advanced life support for more than an hour and was admitted to the intensive care unit of our hospital. In echocardiography a left ventricle severe systolic disfunction was found, without chambers enlargement, nor valvulopathies, nor congenital heart disease features, nor infectious endocarditis signs.

He was born in Guinea Conakry and lived in Spain since 2014 working as farmworker and living in a cottage, at a low income settlement. No consumption of toxic substances or risk habits.

After 30 days of intensive care unit stay, the patient was transferred to the internal medicine ward and developed progressive giant painless subcutaneous soft tissue purulent collections, without fever, erythema, nor otherwise septic or inflammatory signs, but with soft tissue deformity. The purulent collections were located as single giant collections, at the right hand dorsum, and at the anterolateral soft tissue surrounding the left shin (Figure 1), and the right shin.

After a positive culture was obtained, levofloxacin 500 mg q.d. and doxycicline 100 mg b.i.d were prescribed for one month, the right-hand collection was resolved after fine needle aspiration, and surgical drainage was needed for healing the legs collections. Once the severe soft tissue infection was cured, the patient was doing well, able to take care of himself, ate and walked alone, but with a loss of ability and strength in his right hand, and had no heart failure symptoms. An automatic defibrillator was implanted, and the patient was discharged from the hospital after a 105 days hospital stay, with heart failure with reduced ejection fraction standard treatment.

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Fine needle aspiration was made in all the collections, obtaining abundant thick brown pus, that was sent to the microbiology laboratory for staining and cultures (Figure 2).

Gram staining of the right hand dorsum collection showed numerous polymorphonuclear leukocytes and no visible microorganisms. However, 4 days of incubation on blood agar at 35°C under 5% CO_2 resulted in the formation of pinpoint-sized colonies resembling water droplets. These colonies could not be identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) ("no peaks found"). Gram and Ziehl–Nielsen stainings performed on the colonies showed no bacteria. These results led us to suspect *Mycoplasma* spp, and the culture were transferred to Reference Laboratory for ARNr16s PCR and subsequent sequencing, where this microorganism was detected and identified.

Two weeks later collections obtained from the leg were

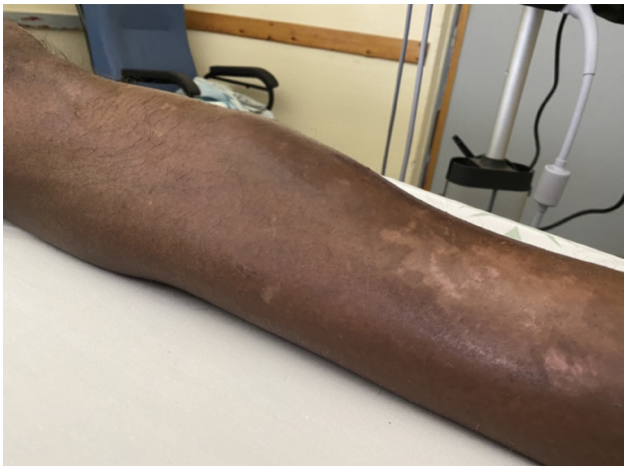

Figure 1 | **Left leg soft tissue collection**

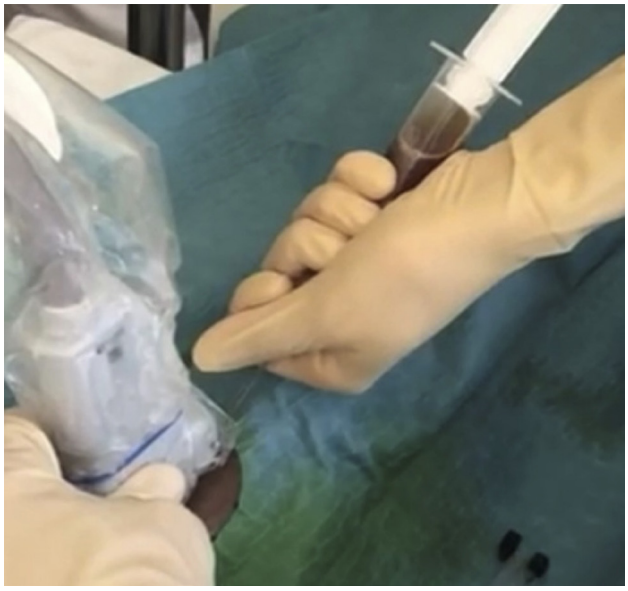

Figure 2 | **Left leg fine needle pus aspiration**

also cultivated but, although the incubation period was prolonged, no bacteria grew; probably due to the stablished antimicrobial therapy with levofloxacin. The sample was sent to Reference Laboratory for ARNr16s PCR and the result was positive to *Mycoplasma hominis*.

Mycoplasma species are smaller than most bacteria and are distinguished by the lack of a cell wall. These microorganisms present fastidious growth requirements for detection under culture conditions. Because of their small cell size, they usually do not even produce turbidity in broth cultures and routine conditions may fail in the isolation of this kind of bacteria.

M. hominis may exist as commensals primarily associated with mucosa in the urogenital tract of healthy humans. It is generally responsible for pelvic inflammatory illnesses, postpartum and neonatal [1], or genital trauma related infections [2]. The infections outside the genitourinary tract occur rarely, but *M. hominis* has been reported to cause different kind of deep tissue infection, including mediastinitis [3], endocarditis [4], abscesses (perirectal [5], perinephric [6], brain [7], periaortic [8], multiple intrabdominal [9]) and bacteremia [1], particularly in postoperative patients [10], transplant patients [8] and immunocompromised patients [11], althoug it may be underestimated.

Although approximately 50% of patients with extragenital *M. hominis* infections has an impaired cell-mediated immune system or hypogammaglobulinemia, our patient had not. He was admitted to the hospital because a ventricular fibrillation cardiac arrest produced by myocarditis. Lately in the intensive care unit he developed multiple infectious complications, among which was the *M. hominis* infection depicted in this paper. Despite the long-term hospitalization and multiple tests performed, no cause of immunosuppression had been detected. It is possible that infection was originated by *M. hominis* bacteriemia and soft tissue seeding, secondary to a minor urethral mucous injury produced by an indwelling urinary bladder catheter, over a previously infected or colonized urethral mucosa. Depending on the selected population, *M. hominis* urogenital infection or colonization, may have an overall prevalence of 10.74% in men, and 8.83 % in women [12], so these individuals may have a possible risk for bacteremia and deep tissue *M. hominis* infections, in case of urethral catheterization, specially in susceptible patients. More studies are needed to clarify these issues.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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