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COVID-19: Some unresolved issues

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ABSTRACT

Two years after the COVID-19 pandemic, many uncertainties persist about the causal agent, the disease and its future. This document contains the reflection of the COVID-19 working group of the Official College of Physicians of Madrid (ICOMEM) in relation to some questions that remain unresolved. The document includes considerations on the origin of the virus, the current indication for diagnostic tests, the value of severity scores in the onset of the disease and the added risk posed by hypertension or dementia. We also discuss the possibility of deducing viral behavior from the examination of the structure of the complete viral genome, the future of some drug associations and the current role of therapeutic resources such as corticosteroids or extracorporeal oxygenation (ECMO). We review the scarce existing information on the reality of COVID 19 in Africa, the uncertainties about the future of the pandemic and the status of vaccines, and the data and uncertainties about the long-term pulmonary sequelae of those who suffered severe pneumonia.

Keywords: COVID-19, SARS-CoV2, treatment, vaccination, virus origin, diagnostic scores, diagnostic tests, arterial hypertension, dementia, viral genome, drug combination, corticosteroids, ECMO, Africa, future and vaccines, pulmonary fibrosis, sequelae.

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COVID-19: Algunos asuntos no resueltos

RESUMEN

Cuando han transcurrido ya dos años de la pandemia de COVID-19 persisten muchas incertidumbres sobre el agente causal, la enfermedad y su futuro. El presente documento contiene la reflexión del grupo de trabajo sobre COVID-19 del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) en relación a algunas preguntas que nos parecen sin resolver. El documento incluye reflexiones sobre el origen del virus, la indicación actual de pruebas diagnósticas, el valor de los "scores" de gravedad en el comienzo de la enfermedad y el riesgo añadido que supone la hipertensión o la demencia. Se discute también, la posibilidad de deducir del examen de la estructura del genoma viral completo el comportamiento viral, el futuro de algunas asociaciones de fármacos y el papel actual de recursos terapéuticos como los corticoides o la oxigenación extracorpórea (ECMO). Revisamos la escasa información existente sobre la realidad de la COVID-19 en África, las incertidumbres sobre el futuro de la pandemia y la situación de las vacunas y los datos e incertidumbres sobre las secuelas pulmonares a largo plazo de los que padecieron neumonía grave.

Palabras clave: COVID-19, SARS-CoV2, tratamiento, vacunación, origen del virus, scores diagnósticos, pruebas diagnósticas, hipertensión arterial, demencia, genoma viral, combinación de fármacos, corticosteroides, ECMO, África, futuro y vacunas, fibrosis pulmonar, secuelas.

INTRODUCTION

As the sixth wave of the COVID-19 pandemic is heading towards its extinction and after the extraordinary spread of the Omicron variant, it is time to continue thinking on the situation in which we find ourselves in the pandemic. The COVID Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has discussed some of the issues that remain unclarified two years after the beginning of the pandemic among us and despite the fact that hundreds of thousands of scientific papers have been published on it.

It is not possible to be exhaustive and we have selected some questions whose answer seemed to us inconclusive or open to debate on which we have tried to offer our point of view thinking that it may be of interest, first for the members of ICOMEM and also for anyone with concern about this phenomenon.

WHAT IS THE ORIGIN OF SARS-COV-2? NATURAL SELECTION OR LABORATORY MANIPULATION?

There is little doubt that the COVID-19 pandemic originated in the Chinese city of Wuhan. The same authors who proposed the name of the pathogen (SARS-CoV-2) described its close relationship with viruses specific to bats in various regions of China and considered the existence of an intermediate mammal (as yet unidentified) in the virus jump from bat to man. According to them, this jump most likely occurred in the Wuhan market, where the first human cases were identified, and where wild mammalian species are traded [1]. Other Chinese researchers believe that the jump between species may have occurred at a location other than Wuhan [2], however the origin of the pandemic in that city seems undoubted.

The main controversy centers on the way in which the virus developed. The most widely accepted is the passage from the bat to an intermediate animal host, as yet unidentified, prior to transmission to humans. It is also considered the possibility that the virus passed from bat to human, and evolved in asymptomatic transmission to acquire the characteristics that caused the pandemic transmission [3-5]. Finally, the presence of a virology laboratory located in Wuhan, with lines of work on mammalian viruses, raises the possibility that the virus, modified during passage through cell cultures or by different species, could leave the laboratory accidentally. This hypothesis is considered unlikely [3-5], since there have been cases of accidental virus escapes from laboratories in the past [4,6,7], in all of them the outbreak started in workers and relatives of laboratory personnel, something that has not been confirmed in the Wuhan outbreak [8]. The lack of transparency of the Chinese authorities has facilitated the doubts that fuel the controversy. Finally, we believe that the theories of those who posit the intentional release of the virus, in the absence of evidence other than various conspiracy theories, do not merit further attention.

From a practical point of view, and given that there is no doubt about the need for very strict security measures in virology laboratories, this controversy should make us aware of the need to control wildlife trafficking, to enhance epidemiological surveillance and to demand transparency and early communication from the corresponding authorities in all epidemiological events.

WHO SHOULD BE TESTED FOR COVID-19 AT THE PRESENT TIME?

The performance of diagnostic tests for SARS-CoV-2 has two main purposes: a health care purpose, individual, in symptomatic persons diagnosed with COVID-19 who can benefit from specific health care, and a public health purpose, collective, to carry out measures to prevent transmission and help globally to control the pandemic. According to these objectives, the indications for COVID-19 diagnostic tests should be adapted to the epidemiological reality of each moment of the pandemic.

At the present time (March 2022), the characteristics of the pandemic in Spain are conditioned by two main factors: the high vaccination rate in the Spanish population (>90% in the population over 12 years of age) and the characteristics of the disease produced by the SARS-CoV-2 Omicron variant, responsible for practically all infections. These two factors determine, on the one hand, a high incidence, but with a high percentage of asymptomatic individuals (up to 80%-90%) and low severity in symptomatic individuals, assessed by the rate of hospitalizations, ICU admissions and deaths. Mortality due to COVID-19 among vaccinated persons is estimated at 0.003% in our country. It should not be forgotten, however, that certain groups have a higher risk of serious disease. Among them, unvaccinated persons should be considered, especially those of advanced age or with underlying diseases, and immunocompromised vaccinated persons or those of advanced age (>80 years).

With these premises in mind, attempts should be made to rationalize the indications for COVID-19 diagnostic tests to avoid overflowing diagnostic laboratories, optimizing resources, avoiding inconvenience to the population and making inappropriate decisions that may ultimately harm patients.

In our opinion, diagnostic tests should be considered in the situations listed in Table 1.

ARE THERE EVOLUTIONARY "SCORES" CLEARLY SUPERIOR TO THE OTHERS AND OF INDISPUTABLE USE?

The stratification of the risk of poor outcomes is one of the most important tasks of the physician during the initial care of any pathology in order to make the first decisions. COVID-19 has been a challenge in this regard, as we are faced with an unknown disease. Numerous research studies have been published describing variables related to increased mortality [9] and risk stratification models [10-18]. However, the

Table 1 Indication of COVID-19 diagnostic tests at present.

Indication of tests
1.-Symptomatic persons: - Persons with severe symptoms requiring health care. - Persons with mild-moderate symptoms who may benefit from treatment to prevent progression (immunocompromised, unvaccinated or vaccinated elderly (>80 years), unvaccinated persons >65 years with significant underlying disease).
2. Asymptomatic persons: - Persons who are going to undergo immunosuppressive medical procedures, regardless of vaccination status: solid organ or hematopoietic progenitor transplantation, chemotherapy and cancer immunotherapy (individualizable). - May be considered in individuals who are to undergo surgical procedures or aerosol-generating procedures.
Contraindication of tests **We do not consider COVID-19 diagnostic testing indicated in the following situations:**
1. Symptomatic persons: - Persons with mild symptoms who do not benefit from health care. Isolation measures to prevent transmission are of limited effectiveness considering that most transmissions can occur by persons without symptoms. Persons with symptoms should avoid contact with vulnerable persons at high risk for severe disease. - Repeat testing to make decisions, such as the duration of isolation. No laboratory test is efficient in this regard and the decision should be guided by clinical-epidemiological criteria.
2. Asymptomatic persons: - Routine hospital admissions or medical-surgical procedures in groups other than those mentioned above. - Contact studies, in the case of low-risk individuals.

publications include high or uncertain risks of bias [19] due to a combination of the use of retrospective data, poor clinical reporting, and inadequate methodological conduct. A description of the population characteristics included is critical for clinicians to understand whether the proposed model might be appropriate for their population or setting. Unfortunately, published studies often lack this. Moreover, often the available sample sizes and number of events for the outcomes of interest are usually limited, which increases the risk of overfitting the model, so that the performance of these models is likely to be worse than that reported by the investigators. Finally, most do not include external validation of the model.

These risk factors and models have been developed in the unvaccinated population, so their usefulness in the current scenario may not be adequate, since vaccinated individuals have been shown to be at lower risk for a fatal outcome [20]. However, the studies that are beginning to be published with vaccinated populations show that the risk factors are similar to those previously published, although the risk of poor evolution is lower [21-23].

In conclusion, the models published to date raise doubts about their applicability in routine clinical practice. None of them can yet be recommended for widespread use. However, they could be a helpful tool, in conjunction with the clinical judgment of the professional. In routine clinical practice, the attending physician's decision making takes into account the patient's age, comorbidity, vaccination status or susceptibility to poor response to vaccination, time since symptom onset, and laboratory values (such as LDH, ferritin, D-dimer or C-reactive protein) that show the patient's inflammatory status.

Future studies should focus on validating, comparing, improving and updating the available predictive models in order to safely discharge patients and avoid unnecessary admissions.

DO FACTORS SUCH AS HYPERTENSION OR DEMENTIA WORSEN THE PROGNOSIS OF THE DISEASE?

An unquestionable fact is that the burden of morbidity and mortality in COVID-19 falls disproportionately on the elderly and those with comorbidities [24]. In this context, identifying independent risk factors appears as a critical issue, especially if a putative risk factor is highly prevalent. It is estimated that approximately one third of the population in developed and developing countries is affected by high blood pressure (HBP), with more than 60% of the population over 60 years of age being hypertensive [25]. In relation to dementia, the number of people with dementia is projected to increase from 57.4 million cases worldwide in 2019 to 152.8 million cases in 2050 [26]. These figures justify their importance in COVID-19. The first analyses performed in the pandemic by Wu and McGoogan [27], which included 44.672 patients with confirmed COVID-19 showed higher case-fatality rates than the overall rates for cardiovascular disease (10.5%), diabetes (3%), and HT (6%). Subsequently, studies were added that maintained these vascular comorbidity relationships, with HT as an independent risk factor

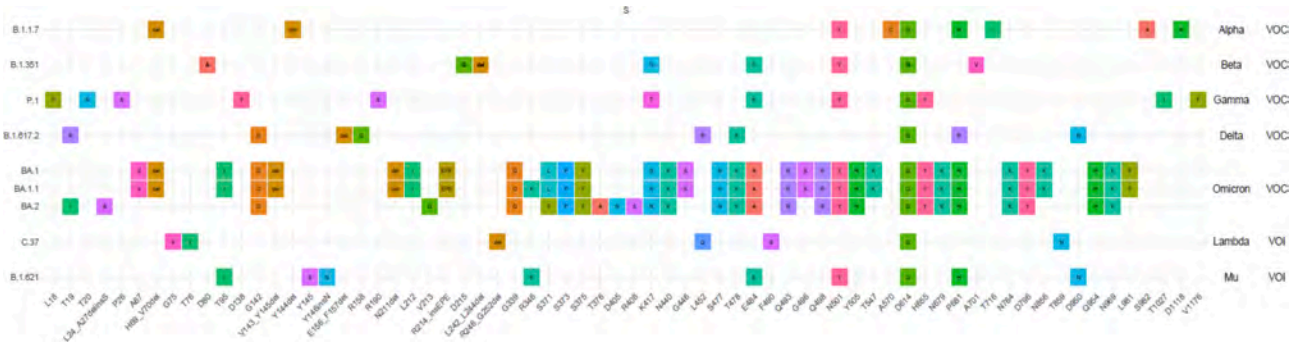

Figure 1 Sequence changes in different variants of concern (VOC) and variants of interest (VOI) (https://www.who.int/docs/default-source/coronaviruse/spike-omicron-ba-1-ba-2.pdf?sfvrsn=d33f5c42_15).

associated with higher mortality, both in meta-analyses [28] as a survival analysis [29]. Finally, data from some studies using multivariate logistic regression models to identify independent clinical predictors of mortality or severity would also support these results. Rodilla et al, in a study with data from 150 Spanish hospitals and 12,226 patients included, showed that HT was associated with an increased risk of mortality due to COVID,19 independently of the sex and age of the patients [30]. But the association between HT and mortality or severity of COVID-19 could also be partly explained by increasing age and higher prevalence of cardiovascular disease, both well-known risk factors for mortality in critically ill patients. Thus, models should be appropriately adjusted to exclude these potential confounding effects [31]. Thus, Sun's study [32] with multivariable model adjusted among 2,304 patients with no other identified comorbidities beyond HT or diabetes, confirmed that HT alone did not increase mortality. In relation to dementia, the mortality rate described for people with dementia, outside of pandemic situations, is three times higher than what would normally be expected for the 5-year average [33]. In a study conducted in England between March 27, 2020 and January 8, 2021, the excess mortality in people with dementia was analyzed and found to be 31% in people over 65 years of age. This, combined with the fact that only 4% of people over the age of 65 have a formal diagnosis of dementia, suggests that COVID-19 has had a disproportionate impact on death in the dementia population [33].

Yang et al. meta-analysis [34], based on 34 studies with adjusted estimated effects, showed that COVID-19 patients with dementia had a significantly higher risk of mortality compared to those without dementia. In multivariate predictive models, dementia also appeared as an independent risk factor for death in COVID patients [35-39].

Currently, frailty is shown to be a good integrative clinical marker of pathological aging. Thus, greater frailty is always associated with poorer health outcomes [40-44] and even as a marker of resource use [45].

In all the studies discussed, biases in the models are possible and it is possible that the factors mentioned that influence mortality do so depending on their intensity, as in the case of the severity of HT or dementia. More global clinical markers such as frailty that better reflect the overall pathological situation associated with aging may be perhaps of better prognostic performance than the different comorbidities taken in isolation.

CAN THE CLINICAL AND EPIDEMIOLOGICAL BEHAVIOR OF A VARIANT BE DEDUCED IN THE LABORATORY FROM THE EXAMINATION OF THE STRUCTURE OF THE COMPLETE VIRAL GENOME?

The evolution of the COVID-19 pandemic has been marked by the successive introduction and global expansion of the so-called variants of concern (VOC) of SARS-CoV-2, with the alpha, delta and more recently omicron variants being the most prominent [46]. Their recognition has only been possible thanks to the large-scale introduction of the so-called next-generation sequencing (NGS) systems in microbiology laboratories and the enormous effort they have put into both sequencing and subsequent bioinformatics analysis.

Each of these VOC is characterized, in addition to its easy transmission capacity, by mutations (change of the original nucleotides for different ones) or deletions (absence of one or several nucleotides) in the RNA sequence and affecting the amino acid sequences in the SARS-CoV-2 proteins [46-48]. The most relevant mutations and deletions are those in the spicule region (protein S). They affect binding to the ACE_2 receptor, the development of specific antibodies, including neutralizing antibodies, and the response to currently used mRNA vaccines designed against the spicule protein of the original Wuhan strain [49]. The sequence of this strain is collected in the GISAID page with the access ID EPI_ISL_402124. Figure 1 shows the amino acid changes present in more than 85% of the analyzed sequences of different VOC and variants of interest (VOI), some of them accumulating more than 35 mutations (https://www.ecdc.europa.eu/en/covid-19/variants-concern). It is important to note that not all amino acid changes in the spicule protein (S) are associated with possible changes in the char-

acteristics of the virus variant and that they can also occur in other regions of the SARS-CoV-2 genome (ORF1ab, ORF3a, E, M, ORF6, ORF6, ORF8 and N). These mutations may eventually affect the secondary and tertiary structure of the S protein and thus its affinity for ACE_2 receptors [50,51].

Given that the number of mutations and the combinations between them are very high, it is difficult to say that the mere presence of a single mutation alone can affect the virulence of SARS-CoV-2. In fact, and although the current scenario with high vaccination coverage in highly developed countries makes it difficult to determine the real extent of the variants, none of the known VOC has a virulence greater than the original Wuhan strain and only the transmission capacity would be affected [52,53]. This idea is reinforced by the fact that the alpha (B.1.1.7), delta (B.1.617.2) and omicron (BA.1) variants only coincide in amino acid changes at two positions (D614G and P681R/P681H). The D614G change arose very early in the pandemic and appears to accelerate virus replication, being present in all the VOC described so far. The mutations at position 861 would be related to the anchoring of the S1 and S2 subunits of the spicule and the better entry of the virus into the cell [52,54].

Some reports have coined the term "mutations of concern" in an attempt to relate their presence to the different characteristics that define VOCs increased transmissibility, increased severity of symptoms and interference with diagnostic techniques, response to treatment or vaccine protection [55]. The most relevant would be those affecting the RBD region of the spicule responsible for binding to ACE_2 receptors that could escape the action of neutralizing antibodies [52]. One of the latest ECDC reports [56] includes as VOC those occurring at spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side) and additional unusual variant-specific changes.

Among the "mutations of concern" the role of position 484 has been highlighted as it is present in both VOC and VOI, E484K in the beta, gamma and mu variants and E484A in omicron. Although not a key position in binding to the ACE2 receptor, mutations at this position have been shown to greatly reduce binding to some of the monoclonal antibodies and result in escape from neutralizing antibodies. Other mutations such as L452R, present in omicron, reduce the affinity for monoclonal antibodies by up to 20-fold [52].

Today, it is difficult to predict whether new mutations will occur that will have an even greater effect on the transmissibility of SARS-CoV-2 as well as its potential virulence. The selection factor for variants remains the number of infected patients, so it is necessary to extend vaccination strategies to all countries. It should also be pointed out that, although the natural tendency of the virus is to lose virulence, mutations or combinations of mutations could arise which by chance could break this rule. For this reason, surveillance for possible new variants should continue, although it is uncertain to be able to predict their characteristics.

ARE DRUG ASSOCIATION STUDIES RELEVANT AND NECESSARY IN DIFFERENT POPULATION GROUPS?

It seems reasonable that pharmacological treatment should be adapted to the evolution of the disease, using antivirals and immunotherapy early on and anti-inflammatory drugs and immunomodulators later on. There are currently a multitude of clinical trials underway trying to identify the most potent drug or the best combination of specific treatment for COVID-19, but we have not yet solved this great challenge.

The drugs and biologics currently available are antivirals (remdesivir, molnupiravir, nirmatrelvir); intravenous immunoglobulins or convalescent plasma, monoclonal antibodies (sotrovimab, bamlanivimab + etesevimab, casirivimab and imdevinab, cignailmab +tixagevimab, BRII-196 and BRII-198), immunomodulators (tocilizumab, sarilizumab, anakinra, canakinumab, baricitinib and tocitinib) and systemic corticosteroids.

Studies on all these therapeutic agents have usually been carried out individually and in isolation and therefore, among those with recognized efficacy, it is pertinent to consider combination studies.

Trials with combination therapies [56-58] suggest that the association of several drugs acting at different times of infection improves prognosis and survival.

Some antiviral drugs (molnupiravir and favipiravir) that act in association on different targets of the reproductive cycle of the virus have demonstrated their efficacy [59]. They have a synergistic effect that allows them to be used at low doses, which reduces side effects and certainly the possibility of generating resistance.

The association of remdesivir with baricitinib has been shown to be better than remdesivir alone in the treatment of patients with COVID-19 pneumonia [60,61]. The combination shortened recovery time, reducing the likelihood of poor outcome and need for invasive ventilation by up to 31%. In addition, the combined treatment was associated with fewer serious adverse events. The largest randomized study conducted by the RECOVERY collaborative group [62] analyzes the effect of tocilizumab in the treatment of 4,116 adult patients hospitalized for COVID-19 disease with hypoxia and systemic inflammation (elevated CRP). The results demonstrate that tocilizumab (immunomodulator inhibitor of the IL-6 response) significantly reduces mortality at 28 days of follow-up, increases the probability of being discharged within 28 days, and in patients who at randomization did not require mechanical ventilation, the probability of requiring mechanical ventilation and mortality was reduced. These benefits are independent of the respiratory support received and of the additional benefit of the systemic corticosteroids administered [62].

Recently, the casirivimab/imdevimab monoclonal antibody combinations (ronopreve, REGEN-COV) [63] or bamlanivimab/etesevimab [64] have been licensed (by emergency procedure) in non-hospitalized patients with mild to moderate COVID-19 at high risk of disease progression. Emerging data on monoclonal antibody combinations are promising, but

more data are needed. The biggest problem at present is their limited availability, which is insufficient to meet the enormous demand that may arise if they prove their prophylactic and therapeutic efficacy.

Despite all the recent progress, there are still many unanswered questions including the clear identification of which agents are most effective for mild, moderate and severe disease, the optimal timing for initiation of therapy, the ideal dose, the duration of therapy and which combination therapy would be most appropriate and beneficial.

WHAT IS THE ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN PATIENTS WITH COVID?

Treatment of adult respiratory distress syndrome (ARDS) in severe cases of COVID-19 is based on invasive mechanical ventilation, muscle relaxation and pronation. When these measures fail, the Extracorporeal Life Support Organization (ELSO) guidelines [65] suggest the use of an extracorporeal membrane oxygenator (ECMO). Prior to the pandemic, there were only two controlled studies for the use of ECMO in ARDS, the CESAR [65] with reduced mortality compared to conventional treatment and the ELOLIA study [66] which showed no impact on 60-day mortality. The 2019 guidelines for the treatment of ARDS recommended its use based on the opinion of an expert center in cases of severe hypoxemia (PaO2/FiO2 < 80 mmHg) and impossibility of protective ventilation despite high PEEP, neuromuscular block and prone decubitus.

The use of ECMO during the SARS-CoV-2 pandemic in critically ill patients admitted to the ICU was between 3 and 11.1%. In the case of ARDS due to COVID-19 we do not have any randomized study evaluating the use of ECMO. The Sociedad Española de Medicina Intensiva, Crítica, y Unidades Coronarias (SEMICYUC) recommends the use of venovenous ECMO (ECMO V-V) in COVID-19 patients in experienced or reference centers, in selected patients with severe ARDS with refractory hypoxemic and/or hypercapnic respiratory failure, in the absence of contraindications, in the absence of response to conventional therapies, especially prone decubitus [66]. The Surviving Sepsis Campaign guidelines for the management of adult patients with COVID-19 disease in the ICU establish a weak recommendation regarding the use of ECMO as rescue therapy, always taking into account the availability of resources and the safety of professionals [67].

Different meta-analyses have been performed on the use of ECMO in patients with COVID 19 with a very high mortality, up to 82%, considering that the high pressure of care during the first wave of the pandemic could have contributed to the poor results. A systematic review published in 2021, which included 1,545 patients with V-V ECMO shows a hospital survival of 49%, with 17.7% of patients still dependent on ECMO at the time of publication. Another systematic review and meta-analysis in 1,986 patients showed that in 98% of cases V-V ECMO was used for respiratory support with an in-hospital mortality of 37.1% similar to that of non-COVID ARDS patients. Age and duration of ECMO were associated with worse prognosis, but not with multi-organ dysfunction as measured by Sequential Organ Failure Assessment (SOFA). Another recent study shows a 40% mortality in COVID 19 and ECMO patients. Age, multiple comorbidities, lower pre-ECMO pH, renal replacement techniques, requirement of vasoactive drugs and bleeding were predictors of death in these patients [68-71].

The series with the largest number of patients included with ECMO (ELSO registry) with data from 1,035 patients with COVID 19 shows a cumulative incidence of in-hospital mortality at 90 days after ECMO initiation of 37% [72]. In France, a retrospective multicenter study of 83 patients showed a mortality of 36.1%, concluding that mortality is similar to that of studies published in the last 2 years in patients with ARDS treated with ECMO [73].

There is still much uncertainty regarding the use of ECMO in COVID-19 patients ranging from the impact of concomitant use of immunomodulators, the possibility of an increased risk of complications such as bleeding, thromboembolic disease or infections in COVID-19 patients, or the long-term sequelae in these patients.

Clinical trials are therefore required to show the effectiveness of the use of V-V ECMO in patients with severe COVID, as well as the impact of certain practices such as the use of prone position, early extubation, adequate anticoagulation or the use of mechanical support of the right ventricle and the impact on long-term morbidity and mortality.

Finally, it is necessary to establish regional strategies that allow equitable access to these techniques [74].

IS THE ISSUE OF THE INDICATION OF CORTICOSTEROIDS AT DIFFERENT TIMES IN THE NATURAL HISTORY OF COVID SETTLED?

Systemic corticosteroids (CS) have been used since the beginning of the pandemic to treat hyperinflammation associated with severe forms of COVID-19, particularly those with pneumonia and ARDS. The role of corticosteroids in the treatment of COVID-19 has generated controversy because of limited rigorous data on their efficacy, optimal doses and regimens, or their effect on disease progression, delayed viral clearance, or secondary infections and other complications [75]. Based on data from large multicenter randomized controlled trials (RCTs), the WHO and other scientific institutions recommend the administration of CS to patients with severe or critical COVID-19 requiring oxygen supplementation, both with conventional oxygen therapy and mechanical ventilation (MV) [76]. In contrast, it is not recommended in patients with non-severe COVID-19, who do not require additional oxygen therapy. These recommendations were made based on the results of the Randomized Evaluation of COVID-19 Therapy (RECOVERY), an open-label, controlled trial that compared a variety of possible treatments in hospitalized patients with COVID-19 [77]. The study showed that administration of 6 mg of dexamethasone

for up to 10 days in patients with COVID 19 with pulmonary involvement reduced 28-day mortality (22.9% vs. 25.7%) in hypoxemic patients, compared to standard practice [77]. The benefit was obtained in patients who were receiving MV at the time of randomization (29.3% vs. 41.4%) or oxygen therapy (23.3% vs. 26.2%), but not in patients without hypoxemia (17.8% vs. 14.0%) [77]. To support the results of the RECOVERY study, the WHO, through the Rapid Evidence Assessment for COVID-19 Therapies (REACT) Working Group, conducted a prospective meta-analysis of 7 RCTs that contained RECOVERY and included 1,703 critically ill patients with COVID-19. The results showed that administration of CS (dexamethasone, hydrocortisone, or methylprednisolone) to hospitalized critically ill patients with suspected or confirmed COVID-19, compared with usual care or placebo, was associated with lower all-cause mortality at 28 days, with no increased risk of serious adverse events [78]. This meta-analysis did not find a greater effect in hypoxemic patients who underwent MV versus those who did not require MV, nor did the effect depend on the duration of symptoms [78].

These findings contrast with the results reported in a series of systematic reviews (SR) and meta-analyses of studies published in the first months of the pandemic, in which treatment with CS did not reduce mortality in cases of severe COVID-19, and in some of them was even associated with higher mortality, longer hospital stay, and a higher rate of bacterial infection and hypokalemia [79-82]. A limitation of these meta-analyses was the absence of RCTs with optimized design and the inclusion of observational studies and case series, which had various confounding factors or biases.

Subsequently, other systematic reviews have been published with a greater representation of RCTs, confirming the beneficial effect of corticosteroids, including a reduction in the mortality rate of patients with severe or critical COVID-19 and the need for mechanical ventilation [83-89]. The Cochrane collaboration updates through an ongoing systematic review approach the evidence on the efficacy and safety of CS in the treatment of people with COVID-19. In the latest update (August 2021), 11 randomized clinical trials with 8,075 participants, completed by April 16, 2021, were included [83]. The results showed moderate certainty evidence for the likelihood of CS slightly reducing all-cause mortality in persons hospitalized for symptomatic COVID-19. In addition, there was low certainty evidence for a reduction in ventilator-free days. No meta-analyses on quality of life and adverse effects were performed, due to high risk of bias, heterogeneous definitions, and lack of information. Nor was it possible to identify published RCTs on non-hospitalized patients with mild or asymptomatic disease treated with CS, so that, at present, there is no evidence in this regard [83]. We identified 42 ongoing and 16 completed but unpublished RCTs in trial registries that point to possible changes in effect estimates and certainty of evidence in the future.

CS have become first-line treatment for hospitalized patients with COVID-19. However there are still unresolved questions regarding the treatment of COVID-19 infection with CS:

There is a need for good quality evidence on the magnitude of effect in specific COVID-19 severity subgroups in which there is greater benefit. Benefit with early administration of CS (<7 days of ARDS onset) on reduction of in-hospital mortality and duration of MV in ARDS cases is demonstrated [75]. The evidence for its use in the context of septic shock associated with COVID-19 remains to be elucidated. Benefit has also been proven in severe cases with hypoxemia with or without the need for MV [77,78]. As for patients with mild to moderate COVID, no reduction in mortality was observed in the RECOVERY study [77]. There is a need to confirm whether CS administration in patients with COVID-19 who do not require oxygen supplementation or respiratory support (first week of the disease course), may be harmful and is associated with delayed viral clearance and increased risk of mortality.

The optimal time to initiate CS therapy in COVID-19 is not well understood. In the RECOVERY study, the mortality benefit was only evident in patients with a symptom duration of 7 days or more [77]. On the other hand, low doses of corticosteroids may not have a significant impact on the duration of SARS-CoV-2 viral shedding [84]. It is necessary to clarify whether there is any subpopulation of infected patients in which the early use of corticosteroids may be justified to prevent progression to more severe forms of COVID-19.

There are doubts as to whether the benefit of CS on mortality is a class effect or there are differences between them. According to the RECOVERY study, such a class effect could exist [77]. However, some published studies establishing direct comparisons between IQs show some discrepancy in relation to this class effect [85-87].

Another aspect that remains unclear is the correct dose. Most published studies, as well as clinical recommendations, use low doses of corticosteroids (dexamethasone 6 mg/day or equivalent doses), which do not seem to have a significant impact on viral clearance. In published studies comparing different doses of corticosteroids, no clinical benefit seems to be shown with high doses of corticosteroids [88-90]. However, there are studies that obtain better results at higher doses [91]. There are also questions about whether higher doses may be beneficial in patients who develop ARDS [92].

In relation to the regimen, some studies have shown an advantage in treatment with corticosteroid pulses versus fixed daily doses, probably due to the activation of the non-genomic corticosteroid pathway [93].

Few studies have reported adverse effects of glucocorticoids in patients with COVID-19. Although adverse event rates appear relatively low, potential side effects should be evaluated to improve patient outcomes.

WHAT IS THE REALITY OF COVID-19 IN AFRICAN COUNTRIES?

Little is known about the extent of SARS-CoV-2 transmission or its impact in Africa. In the absence of data, there is a widespread view that, in Africa, COVID-19 has had little im-

pact. But this idea is generated in the absence of evidence and therefore in the absence of scientific evidence.

There has been much speculation, with the term "African paradox" being used because of the low prevalence of COVID-19. There are different theories that have tried to explain this fact: a high exposure to other coronaviruses that would make them cross-immune, that the population is younger and therefore less vulnerable, or that the experience during the Ebola crisis would have allowed public health agencies throughout Africa to better contain COVID-19 [94] and that certain live attenuated vaccines (BCG vaccine, oral polio vaccine and measles vaccine) would have created non-specific innate immunity that would also protect against COVID-19 [95-97]. But the reality seems very different from these theories and most likely there is an under-diagnosis, with little data available, mainly due to lack of resources. Most of the data on the impact of the pandemic come from South Africa, documenting more than 750,000 cases, more than 20,000 deaths and a case fatality rate of 2.7% [98-100].

In a cross-sectional study, conducted in November 2020 in Nairobi, Kenya [101], including 1,164 individuals, the adjusted seroprevalence was 34.7%. Half of the enrolled households had at least one positive participant. COVID-19 in that study was 2 times more frequent in persons aged 20-59 years than in those aged 0-9 years. Infection case fatality rates were 40 per 100,000 infections, being higher in persons older than 60 years. According to this work, more than one-third of Nairobi residents had been exposed to SARS-CoV-2 in November 2020, but with a case fatality rate 10 times lower than that reported in Europe and the U.S. The national surveillance system detected 2.4% of all SARS-CoV-2 infections in Nairobi, reflecting an underestimation ratio of 42:1.

A paper providing routine surveillance data in Zambia has been published in February 2022 [102]. Since 2017 this group has been conducting systematic postmortem surveillance for respiratory pathogens among deceased infants in Lusaka, Zambia. When the pandemic breaks out, they employ such systems for SARS-CoV-2 detection. The study was conducted from June to September 2020 (3 months). A total of 372 deceased patients were included, with PCR available in 364 (97.8%). SARS-CoV-2 was detected in 58/364 (15.9%) at the recommended cycle threshold value of <40 and in 70/364 (19.2%) when amplified at any PCR detection level. None of the patients were tested before death. The prevalence of mortality in Zambia, based on the data reported in this paper, is surprisingly high. Deaths from COVID occurred across a broader age spectrum than reported elsewhere and were concentrated in persons younger than 65 years, aged 20 to 59 years. Ten percent (7/70) of deaths occurred in children, including three infants. No differences by sex were found. The most common conditions were identified in at least 10% of the cohort: tuberculosis (31%), hypertension (27%), HIV/AIDS (23%), alcohol consumption (17%) and diabetes (13%). This study, with limitations but well conducted, puts the spotlight on the need to establish prevalence in this continent, because if the data obtained were generalizable, the impact of COVID-19 in Africa would have been considerably underestimated.

WHAT ARE THE MAIN UNCERTAINTIES IN THE VACCINE ISSUE?

The uncertainties have to do with the evolution of the pandemic itself, the characteristics of the vaccines and the resulting immunity. The well-documented historical experience of how and when respiratory virus pandemics ended is very limited and corresponds mainly to influenza pandemics. The two major pandemics, the "Russian" influenza pandemic at the end of the nineteenth century [103] and that of the 1918 influenza, ended in the absence of vaccines, and the return to normal life occurred very quickly. However, it is not known what exactly was the virus causing the "Russian" pandemic and why both pandemics were relatively short-lived: the "Russian" one had only a few waves in about four years, and the 1918 one had three waves in three years. It seems that the H1N1 virus responsible for the 1918 pandemic continued to circulate until 1957, and then disappeared and re-emerged in 1977. The reasons for this behavior of the virus are also not well known. For all these reasons, we do not know when or how the coronavirus pandemic will end. We do not know when, partly because we do not know whether a new variant will be selected that, in addition to being highly transmissible (in order to replace omicron), has some escape from the immunity generated by natural infection or vaccination. And we do not know how, i.e. whether the virus will disappear or whether, as seems more likely, it will remain with us endemically, and perhaps manifest itself mainly in winter when people concentrate their lives indoors.

If SARS-CoV-2 infection remains endemic (most likely because there is beginning to be evidence of animal reservoirs, such as deer), it seems reasonable to maintain a medium- to long-term vaccination strategy. The question is who to vaccinate, how often to vaccinate, and with what type of vaccines. If the severity of infection in the population as a whole is similar or less than that of omicron, it seems reasonable to revaccinate (or give booster doses) only to those who are vulnerable to the most severe forms of the disease, because: a) they have a certain degree of immunosuppression accompanied by a poor response to vaccination, or b) even if they have a good response to previous vaccination, they are very old and have high comorbidity that causes them to lose immunity fairly quickly. In the rest of the population it would not be essential to revaccinate or administer a booster, because there is accumulating evidence that cellular immunity (the most important to avoid severe disease) is reasonably well maintained for a long time against all known variants of SARS-CoV-2, and is improved with repeated contact with the virus or vaccine boosters [104-106].

The frequency of vaccination or booster will depend on the duration of immunity in vulnerable persons, on the appearance of new variants with certain vaccine escape, and on the interaction between these last two variables. It is too early to tell, but from recent experience on the loss of vaccine effectiveness with the usual vaccines so far and especially the high efficacy of boosters reducing symptomatic and severe infec-

tion, it is possible that the frequency should be at least annual. Finally, the ideal is to use sterilizing vaccines, because they reduce the risk of infection (and therefore community transmission) more than the current ones, which are only neutralizing; but sterilizing vaccines have not yet been fully developed, nor their efficacy tested, nor their costs evaluated. In the medium term, emphasis should be placed on vaccines that are easy to store, that generate longer-lasting protection than the current ones derived from mRNA technology, that are simple to manufacture and less costly, such as some based on traditional technologies that are being approved very recently. Finally, they should protect against any new variant of SARS-CoV-2. We will see if all this comes to fruition.

WHAT DO WE KNOW ABOUT THE LONG-TERM IMPACT OF COVID-19 ON LUNG FUNCTION?

One of the major medium and long-term complications in patients who have suffered SARS-CoV-2 infection is the development of interstitial disease with pulmonary fibrosis, whose pathogenesis is linked to the existence of acute respiratory distress syndrome, but in which capillary thrombosis, drug toxicity and, where appropriate, the use of ECMO could also be involved. This had already been reported in relation to outbreaks of SARS-CoV-1 and MERS, in which series of patients followed over the long term have shown the presence of radiological alterations or functional deterioration in up to 30% of patients with a history of hospitalization with or without admission to the ICU [107,108].

The radiological pattern of interstitial disease with ground glass image and fibrosis appears already at the time of discharge, mainly, but not exclusively, in patients who have survived severe and critical illness. Studies published at the beginning of the pandemic show that between 50 and 75% of patients who suffered severe or critical illness have alterations in pulmonary function in the first month after discharge [109, 110] and that this alteration is related to the degree of radiological involvement. Already in studies at 3-4 months after discharge, the radiological alteration figures are higher than 45% with pulmonary function alteration ranging between 20 and 70%, but this depends on the severity of the acute disease [111]. Thus, in a study carried out in patients with mild disease and previous normal lung function, no functional alterations were observed at 3 months after the disease [112]. In studies stratifying by severity, the occurrence of interstitial disease is clearly related to the severity of the disease, such that in severe and very severe patients, severe fibrosis is observed above 35%, while in moderate disease, interstitial changes are mild [113,114]. In very severe and critical patients discharged from the ICU, the number of radiological and functional alterations in some series reaches up to 50% of the cases [115].

One of the most important series available is that of the Spanish CIBERESUCICOVID study, with 1,255 patients discharged from the ICU, for whom 3-month follow-up data have been published. In 65% of the cases, diffusion capacity alteration persists and more than 93% of the cases present radiological alterations in the CT, with 10% of totally established fibrosis and around 15% with persistent interstitial infiltrate [116]. A substudy published by one of the participating hospitals shows even higher figures of pulmonary fibrosis, reaching 21% and ground glass pattern in 30% [117]. Also from the CIBERESRESUCOVID cohort, there are recent data from a subgroup of 67 subjects showing fibrosis data at 6 months in CT, with figures above 30% and already without any modification in relation to the previous data at 3 months [118]. Another series, with data at 6 months, confirms a high incidence, between 30 and 50%, of pulmonary fibrosis with functional impairment in very severe patients, with lower figures of 20% in patients with moderate disease [119].

The figures are confirmed in studies that are primarily radiological based but which relate imaging changes to functional impairment and find established fibrosis patterns in 35% of patients, most of whom also have impaired diffusion capacity. when the studies are exclusively radiological [120]. Finally, we have at least one series of patients with follow-up at 3, 6, 9 and 12 months. These patients, severe but not requiring invasive mechanical ventilation, at 12 months presented a ground glass interstitial pattern in 24% of the cases, with altered diffusion capacity, but not severe fibrosis. Of greatest interest is that the changes did not change after the 9th month of life [121].

As for the treatment of post-COVID-19 pulmonary fibrosis, the drugs used in the treatment of idiopathic pulmonary fibrosis are being used in practice, but there is no evidence of their efficacy. A population-based study conducted in Korea has shown that idiopathic pulmonary fibrosis is associated with an increased incidence of COVID-19 [122] and very recently a bioinformatics analysis study has hypothesized that post-COVID fibrosis may share gene networks with idiopathic pulmonary fibrosis [123]. Studies are underway to evaluate the efficacy of pirfenidone (IL-6 inhibitor) and nintedanib (IL-1 inhibitor) [124] and other molecules with antifibrotic capacity [125]. In patients with terminal disease, the therapeutic option is transplantation, although so far the number of reported cases of this procedure in patients with post-COVID lung lesions is not high. Only one case has been reported in Spain, which has not been published in scientific journals. We have a multicenter and multinational series of 12 cases, with good results [126] and very recently a large American series has been published with 214 cases of COVID-19 patients transplanted between October 2020 and September 2021, which corresponds to 7% of the total number of transplants performed in the United States in that period of time. Of these, 140 cases were performed in unresolved acute situation and 74 in already chronic fibrosis. It should be noted that 118 patients were on ECMO and 97 on mechanical ventilation. Survival at 3 months was 95%, which should be considered a good result [127]. There is no doubt that transplantation has to be considered in end-stage lung disease secondary to COVID-19 and some clear protocols for its performance have already been published [128].

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Documento de opinión de expertos para la mejora de la cobertura vacunal frente a la gripe estacional

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RESUMEN

La gripe estacional sigue siendo un importante problema de salud pública, y la vacuna antigripal es la medida más efectiva para su prevención. En nuestro país, los datos de coberturas vacunales de las últimas temporadas muestran unas tasas de vacunación muy por debajo de los objetivos marcados por los organismos oficiales. Tras la pandemia de la COVID19, las coberturas vacunales para la gripe han experimentado una notable mejoría. Dado que resulta imperativo alcanzar y mantener unas elevadas tasas de vacunación con el fin de evitar el impacto clínico y económico de la gripe, un grupo multidisciplinar de expertos en el área de las vacunas hemos analizado cómo afectan las bajas coberturas en nuestro país y hemos diseñado una serie de medidas para incrementar la cobertura vacunal de la gripe, especialmente en los colectivos definidos como prioritarios.

Palabras clave: Gripe, vacuna antigripal, reticencia a la vacunación, eventos cardiovasculares, enfermedades respiratorias, ancianos, profesionales sanitarios.

Expert opinion on strategies to improve vaccination coverage against seasonal influenza

ABSTRACT

Seasonal flu continues to be a major public health concern, and the influenza vaccine remains the most effective preventive measure. In Spain, vaccination coverage data from previous seasons show vaccination rates well below official targets; however, these figures improved significantly after the COVID-19 pandemic. Given the importance of achieving and maintaining high vaccination rates in order to avoid the clinical and economic impact of influenza, our multidisciplinary group of experts on vaccines analyzed the impact of low vaccination rates in Spain and drafted a series of measures to boost influenza vaccination coverage, particularly among priority groups.

Keywords: Influenza, influenza vaccine, vaccine hesitancy, cardiovascular events, respiratory disease, elderly, health care professionals

INTRODUCCIÓN

La gripe estacional es todavía a día de hoy un problema de salud mundial debido a su elevada morbimortalidad, con hasta 650 000 muertes anuales reportadas en el mundo [1]. Se trata de una enfermedad respiratoria aguda que produce una afectación sistémica causada principalmente por los virus de la gripe tipo A y B [1]. Su elevada variabilidad antigénica y su capacidad de evolución permiten que sigan manteniendo su virulencia. Aunque en la mayoría de los casos se presenta de forma leve y autolimitada, puede evolucionar a formas graves o complicadas e incluso llegar a ser letal.

En España, durante la temporada 2019-2020 se estimaron 619 000 casos confirmados de gripe que acudieron a las consultas de atención primaria, 27 700 hospitalizaciones con gripe confirmada por el laboratorio, 1 800 ingresos en la unidad de cuidados intensivos (UCI) con confirmación por laboratorio y 3 900 muertes atribuibles a esta enfermedad [2]. Los mayores de 65 años fueron los más afectados y supusieron el 47 % de los casos graves hospitalizados confirmados de gripe [2].

La vacuna frente a la gripe es la medida más efectiva para prevenir la enfermedad y sus complicaciones. Su efectividad global se sitúa en torno al 65 %, pero varía en función de

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las características de la vacuna, del virus (variación antigénica/cepa circulante), de la población (edad, comorbilidades, infecciones previas, vacunación anterior) y del objetivo que se persigue alcanzar (diagnóstico confirmado, enfermedad clínica, complicaciones o fallecimientos) [3]. Asimismo, las vacunas antigripales tienen buenos perfiles de seguridad y se han reportado pocos efectos adversos [4]. A pesar de esto, las tasas de vacunación se han reducido en los últimos años y las coberturas vacunales para la gripe estacional varían en función de los países entre menos del 1 % hasta más del 75 % en las personas de 65 y más años, mientras que para las personas con enfermedades crónicas y el personal sanitario la cobertura es inferior al 40 % en la mayoría de los países [5]. En nuestro país, solo un 22,5 % de las personas de entre 60 y 64 años se vacunó en la temporada 2018-19 [6]. Con respecto al personal sanitario, esa misma temporada se reportó únicamente un 35 % de cobertura vacunal [6]. Las bajas coberturas no solo reducen el número de personas vulnerables que estarían protegidas durante las epidemias anuales de gripe, sino que además pueden afectar negativamente la capacidad de producir vacunas en caso de una pandemia.

La temporada pasada, 2020-2021, la gripe convivió con la pandemia mundial de la COVID-19. En este escenario, las tasas de vacunación aumentaron significativamente y se alcanzaron valores de cobertura vacunal de más del 65 % en los mayores de 65 años, del 40 % en las personas de entre 60 y 64 años y del 62 % entre el personal sanitario [7].

Teniendo en cuenta este contexto, un grupo multidisciplinar de expertos relacionados con la vacunación, en el que se incluyen profesionales médicos de medicina preventiva, pediatría, medicina interna y atención primaria, y de enfermería de atención primaria, hemos analizado el impacto a nivel sanitario que pueden tener unas bajas coberturas vacunales en nuestro país y, por otra parte, cómo ha influido la pandemia de la COVID-19 en el aumento de estas coberturas. Finalmente, hemos propuesto una serie de medidas para tratar de mantener elevadas las tasas de vacunación en las próximas temporadas.

ANÁLISIS DEL GRUPO DE EXPERTOS

Coberturas vacunales prepandemia. Desde el año 2011-hasta la pandemia de la COVID-19 en el año 2019, la media de cobertura vacunal de gripe a nivel nacional sólo fue superior al 50 % en el colectivo de mayores de 65 años, con un mínimo del 54,3 % y un máximo del 57,7 % en este periodo. A partir del año 2017 se registraron también los datos de cobertura vacunal de otros colectivos como las personas de 60 a 64 años, las mujeres embarazadas y los profesionales sanitarios. La cobertura vacunal de las personas entre 60 y 64 años en este periodo (2017-2019) fue del 22,1 % y 22,3 % respectivamente [6,8]. En estas dos temporadas únicamente se vacunaron el 31,1 % y el 35 % de los profesionales sanitarios [6,8].

Una de las posibles causas de las bajas coberturas vacunales en España es la falsa percepción que tiene la población general sobre la gripe como una enfermedad leve [9]. Por un lado, se trata de un virus que se puede confundir con otros virus estacionales que producen una sintomatología más leve y menos complicaciones asociadas, como los del catarro común (rinovirus) [10]. Además, dado que la mayor parte de la población clasificada como sana no desarrolla una infección grave como consecuencia de la gripe, ni presenta complicaciones asociadas, esto promueve de nuevo la sensación de que se trata de una enfermedad poco grave. Sin embargo, la vacuna antigripal impacta positivamente sobre la supervivencia en la población de riesgo (definida como mayores de 65 años y pacientes con enfermedades crónicas previas) y reduce las infecciones graves y complicaciones asociadas a la infección por la gripe [11]. Esta puede ser la razón por la que esta población presente un mayor porcentaje de tasas de vacunación y de que dichas complicaciones se hayan visto reducidas.

En este grupo de trabajo consideramos que la falta o ausencia de confirmación diagnóstica de la infección por gripe mediante una prueba rápida o un análisis microbiológico en atención primaria (AP) es otra posible causa que puede estar contribuyendo a que la tasa de vacunación se esté viendo reducida ya que implica un infra diagnóstico que no visibiliza la carga real de la enfermedad. Además, el hecho de que la gripe no aparezca como motivo de defunción en pacientes con patologías previas agravadas por esta patología, contribuye a no valorar la gravedad de la enfermedad. En atención primaria es donde más casos se tratan de gripe y, al no realizarse dicha prueba, se desconoce la tasa real de incidencia.

Por otra parte, existe una desconfianza creciente sobre la efectividad de la vacuna antigripal. A pesar de las múltiples evidencias científicas que han demostrado su eficacia/efectividad y que respaldan el uso de las vacunas, la tasa de vacunación en muchos países sigue siendo insatisfactoria [5]. De hecho, y de forma preocupante, en los últimos años ha crecido una actitud antivacunación y la reticencia o rechazo al uso de vacunas es cada vez más prevalente [12]. Esto se atribuye a la existencia de creencias y mitos que están arraigados en la sociedad y fomentan la vacilación ante el uso de las vacunas. De hecho, según señala la Organización Mundial de la Salud (OMS), se trata de una de las principales amenazas para la salud pública [13].

También existen datos que indican que los profesionales sanitarios perciben la vacuna antigripal como poco efectiva [14]. A pesar de que los ensayos clínicos han demostrado una elevada eficacia para la vacunación frente a la gripe, los resultados de efectividad en los estudios en vida real presentan una elevada variabilidad debida principalmente a las diferencias de diseño entre los diferentes estudios; a factores relacionados con el virus (transmisibilidad, virulencia, comportamiento epidemiológico); de la vacuna (grado de concordancia entre las cepas de la vacuna y las circulantes esa temporada [15,16], tipo de vacuna -atenuada o inactivada-, presencia de adyuvantes y vía de administración), así como factores del huésped (edad, comorbilidad, riesgo de exposición). Esta he-

terogeneidad en los resultados de efectividad vacunal podría condicionar negativamente la opinión de colectivos como el de los sanitarios [3,17].

Impacto clínico de las bajas coberturas vacunales. La gripe estacional está asociada a una elevada morbimortalidad, con 290 000 a 650 000 de muertes debidas a la gripe cada año a nivel mundial [1]. En nuestro país, durante las temporadas de 2015 a 2020, la tasa media acumulada de hospitalización de casos graves de gripe (CGHCG) fue del 20,04 %, reportándose la tasa máxima en la temporada 2017-2018 con un 28,1 % [2,18-21]. Del total de CGHCG en estas cinco temporadas el porcentaje de pacientes que ingresó en UCI fue similar, con una media global de 25,3 %, llegando a alcanzar el 35,1 % en la temporada 2016-2017 [2,18-21], con una letalidad media, estimada en términos de defunciones, del 15,36 % [2,18-21].

El impacto de la infección por el virus de la gripe es especialmente importante en la población con patologías previas como enfermedad cardiovascular, respiratoria, metabólica y renal [22-26]. Se trata de enfermedades crónicas muy prevalentes con una elevada tasa de mortalidad [27-30]. La infección por gripe se asocia a un peor pronóstico de estas enfermedades y los pacientes que experimentan complicaciones tienen una mayor morbimortalidad asociada [22-26]. Con respecto a las enfermedades cardiovasculares y respiratorias crónicas, se ha descrito que la infección por el virus de la gripe incrementa el riesgo de sufrir un infarto y accidentes cerebrovasculares [31]. Específicamente, la gripe aumenta entre 6 y 10 veces el riesgo de sufrir un infarto de miocardio, y entre 3 y 8 veces el riesgo de accidentes cerebrovasculares [31-33]. Además, también exacerba la sintomatología y la progresión de la enfermedad pulmonar obstructiva crónica y el asma [34]. Consecuentemente, la gripe provoca un aumento de la morbilidad y mortalidad hospitalaria en estos pacientes, así como un incremento de los costes y recursos sanitarios, debido a un mayor número de hospitalizaciones e ingresos en unidades de cuidados intensivos (UCI) [22,35,36]. En esta línea, en el último informe del Sistema de Vigilancia de la gripe en la temporada 2019-2020, los factores de riesgo más frecuentes asociados a la aparición de complicaciones hospitalarias en pacientes hospitalizados por gripe fueron la enfermedad cardiovascular previa (34 %), la enfermedad respiratoria previa (28 %) y la diabetes (28 %) [2].

La vacunación frente a la gripe es la mejor forma de asegurar la protección frente a la infección y de prevenir las complicaciones asociadas. Se estima que la vacuna antigripal disminuye el riesgo relativo de infarto de miocardio entre un 15 % y un 45 % [37]. Varios ensayos clínicos y metaanálisis han demostrado también que la vacuna es eficaz en la prevención secundaria de aparición, hospitalización y mortalidad por eventos cardiovasculares [38-42]. Asimismo, con respecto a las enfermedades crónicas respiratorias, la vacunación reduce el número de sobreinfecciones bacterianas y contribuye a la reducción del número de hospitalizaciones y a la disminución del riesgo de muerte [43-45].

Efecto de la pandemia de la COVID-19 en la cobertura vacunal. Siguiendo las recomendaciones de la OMS, el Ministerio de Sanidad propuso unos objetivos de vacunación muy exigentes para la campaña 2020-21, con un 75 % en la población de más de 64 años, en los sanitarios de primera línea de atención a personas infectadas y en los profesionales de centros sociosanitarios, y un 60 % en mujeres embarazadas y personas con factores de riesgo entre 6 meses y 64 años [46]. Aunque solo se ha conseguido alcanzar el objetivo en el grupo de mujeres embarazadas, las coberturas han aumentado significativamente esta temporada [6,7]. Resulta especialmente llamativo el aumento de la cobertura vacunal en el grupo de personas con edades comprendidas entre 60 y 64 años, que se ha incrementado hasta un 40 %, así como las coberturas del 62 % alcanzadas en el grupo de personal sanitario [7].

El aumento de las coberturas vacunales que se observó la pasada temporada se puede atribuir, entre otras causas, a una mayor concienciación de la importancia de las vacunas entre la población [47]. Debido a la pandemia por la COVID-19, la población general ha tenido más acceso a la información sobre vacunas a través de diferentes escenarios como los medios de comunicación o desde las administraciones sanitarias [48]. Además, la COVID-19 plantea en la población la percepción de vulnerabilidad frente a las enfermedades transmisibles, sobre todo en los países desarrollados en los que la incidencia y la mortalidad por estas enfermedades en la población general son menores [49,50]. Por otro lado, el mensaje enviado por las autoridades sanitarias en el que se informaba del riesgo clínico que podría implicar el sufrir a un tiempo ambas patologías y como consecuencia la sobrecarga de los recursos asistenciales puede haber ayudado también al incremento de la cobertura vacunal, especialmente en los grupos de riesgo y en los profesionales sanitarios [48].

Otro punto que considerar es el cambio que ha supuesto la pandemia de COVID-19 en los sistemas de vigilancia de la gripe y de otros virus respiratorios en nuestro país. La llegada de la COVID-19 en el año 2020 produjo una importante distorsión en el funcionamiento de estos sistemas. Como consecuencia, y siguiendo las indicaciones del Centro Europeo para la Prevención y el Control de las Enfermedades (ECDC) y la OMS, se han creado sistemas de vigilancia de infección respiratoria aguda que incluyen de forma conjunta la vigilancia para la gripe, la COVID-19 y otros virus respiratorios como el virus respiratorio sincitial (VRS) [51]. Sin embargo, según establecen instituciones relevantes como el ECDC, en el caso concreto del VRS la infección por este virus no es de notificación obligatoria en la mayoría de los países de Europa [52]. De hecho, los datos se recogen de manera voluntaria por los distintos países en el sistema TESSy (*The European Surveillance System*), un sistema muy flexible basado en metadatos para la recogida, validación, limpieza, análisis y difusión de datos [53]. Adicionalmente la mayoría de los países del espacio económico europeo ya disponen de vigilancia activa y la suficiente capacidad para analizar muestras de laboratorio que podría utilizarse para identificar VRS, pero las definiciones y

los métodos de laboratorio deberían estandarizarse para poder ser consolidados [52]. En general, el sistema de vigilancia de VRS de preferencia será la vigilancia centinela activa, con pacientes de atención primaria y hospitalarios a los que se les toma muestras y se analizan de manera sistemática [54].

En el caso concreto de España la vigilancia virológica de la gripe se complementa con la vigilancia no centinela del VRS desde 2006-2007 y de un sistema de vigilancia centinela y no centinela para el SARS-CoV-2. Esto ha permitido disponer de información de la estacionalidad y de la epidemiologia de estos virus respiratorios a nivel nacional [51]. Con respecto al VRS, el desarrollo de nuevas vacunas y anticuerpos monoclonales enfatizan la necesidad de un sistema de vigilancia fiable para este virus. Disponer de un sistema de vigilancia especifico de VRS es una prioridad, tanto como para estimar la carga del sistema sanitario como para medir el impacto de las futuras estrategias de inmunización frente al VRS [54].

En resumen, como resultado de la pandemia, se han implementado mecanismos de prevención para estas enfermedades, como puede ser la vacunación frente a la COVID- 19 y una mayor concienciación sobre el VRS debido a la mayor disponibilidad de datos epidemiológicos. Estas medidas tendrán, especialmente en el caso de la COVID-19, un efecto positivo sobre las coberturas antigripales al permitir una posible coadministración y también a un incremento de concienciación con la vacunación, especialmente en los grupos de riesgo. En el caso concreto del VRS es más complejo anticipar la posible influencia en las coberturas vacunales de gripe al no disponer actualmente de estrategias preventivas que permitan una vacunación universal en lactantes o adultos.

Grupos objetivos para mejorar las coberturas vacunales. A pesar de ser el que mayor porcentaje de cobertura presenta [7], el grupo de personas mayores de 65 años continua siendo uno de los grupos prioritarios a vacunar. Se trata del colectivo con mayor riesgo de presentar complicaciones a causa de la gripe, y, consecuentemente, una mayor morbimortalidad asociada. Además, se debe tener en cuenta que muchas de las personas ancianas sufren un deterioro funcional durante los ingresos hospitalarios de los que no se recuperarán a pesar de haber resuelto la enfermedad, de manera que la gripe puede acelerar el declive de la situación funcional [55]. Eso, juntamente con la fragilidad y las múltiples comorbilidades presentes en este grupo de población se relacionan con una pérdida importante de la calidad de vida.

Por otra parte, la inmunosenescencia que acontece a partir de los 65 años provoca que la inmunogenicidad de la vacuna de la gripe sea menor en este grupo de población [56]. El empleo de vacunas más inmunógenas y efectivas que generen una mayor protección frente a las cepas circulantes, y con un perfil de seguridad adecuado, garantizarían una mejor cobertura vacunal en esta población. De hecho, diversos estudios han demostrado que la vacuna inactivada de virus fraccionados de alta dosis es una alternativa más inmunogénica y eficaz en la prevención de la infección por el virus de la gripe y sus complicaciones asociadas en la población de edad avanzada con respecto a las vacunas de dosis estándar [57-59] Existe pues una amplia evidencia científica que corrobora la idoneidad de estas vacunas en este colectivo, basada en la consistencia y robustez de los datos obtenidos en los múltiples estudios a lo largo de diferentes temporadas de gripe [56,58].

Las mujeres embarazadas tienen también más riesgo de sufrir complicaciones tras la infección por gripe [60]. En España, se ha estimado que el embarazo incrementa ocho veces el riesgo de hospitalización por gripe. La vacuna de la gripe ha demostrado un múltiple beneficio en este colectivo. En la madre, es beneficiosa en cualquier trimestre de la gestación, pero especialmente en el tercer trimestre, cuando existe una leve inmunosupresión junto a una limitación física evidente como es la reducción de la capacidad pulmonar [61]. También presenta ventajas sobre el feto, dado que la infección por el virus de la gripe durante el primer trimestre se ha asociada a un aumento de malformaciones cardiacas, labio leporino y defectos del tubo neural, y durante el segundo y tercer trimestre a un mayor número de abortos y partos prematuros. Así, la vacunación frente a la gripe reduce en un 40 % la posibilidad de un aborto y en un 45 % la de muerte fetal provocada por esta enfermedad [61,62]. En el neonato (durante los primeros 6 meses de vida) la vacunación de la embarazada consigue evitar el 75 % de los casos graves hospitalizados por gripe [63]. Además, la vacunación de las embarazadas también protege a los posibles convivientes vulnerables disminuyendo las posibilidades de transmisión. A pesar de todos estos datos, la cobertura vacunal de las mujeres embarazadas en las temporadas preCOVID-19 ha estado por debajo de los objetivos, con un 29,4 % en la temporada 2017-2018 y un 40,6 % en la temporada 2018-2019 [6-8].

Entre los profesionales sanitarios, otro de los grupos prioritarios a vacunar, las tasas de vacunación han sido especialmente bajas en los últimos años, si bien se han incrementado a consecuencia de la pandemia de la COVID-19 [7]. Los motivos por los que este colectivo muestra reticencia a la vacunación han sido objeto de estudio durante los últimos años, tanto internacionalmente como en nuestro país. Las múltiples investigaciones, que incluyen desde metaanálisis hasta estudios unicéntricos regionales, coinciden en que la actitud ante la vacunación en las temporadas previas es un factor predictor de una mayor vacunación, así como convivir con personas de riesgo, y el miedo a enfermar o a contagiar a los pacientes [64]. Además, un estudio descriptivo realizado en la Comunidad Valenciana que comprende tres temporadas (2011-2014) concluyó que existen diferencias significativas entre los profesionales que se vacunan siendo los facultativos los menos vacunados y el personal de enfermería el que presenta una mayor cobertura vacunal [65]. Por tanto, resulta imperativo en este colectivo mejorar la cobertura vacunal y concienciar del papel que representa el personal sanitario como potenciales transmisores de la infección por virus de la gripe a pacientes y familiares.

PROPUESTAS DE MEDIDAS PARA MEJORAR LAS COBERTURAS VACUNALES (TABLA 1)

Medidas centradas en la población general

- Estudiar los colectivos que han aumentado su tasa de vacunación en la última temporada y sus motivaciones para vacunarse con la intención de fidelizarles.
- Aplicar en las campañas de vacunación de gripe estrategias más impactantes cómo las usadas por la Dirección General de Tráfico (DGT) en la prevención de lesiones externas por accidentes de tráfico, con el objetivo de concienciar de la importancia de la vacunación.
- Ahondar en las causas y en los motivos por los que la población decide no vacunarse, para plantear posteriores intervenciones, incidiendo en esos motivos para conocer el impacto en la vacunación. En esta línea, y de acuerdo con las propuestas de la OMS [66], sería importante realizar estudios coste-beneficio de la vacunación y dar a conocer a la población general los costes asociados a la morbimortalidad asociada a la gripe y el ahorro estimado de los casos evitados gracias a la vacuna.
- Fomentar el uso en todos los niveles asistenciales de test serológicos de diagnóstico rápidos y de fácil manejo de gripe, VRS y otros virus que causen enfermedades con una sintomatología similar, con el objetivo de concienciar a la población de la elevada incidencia real de gripe.
- Generar y difundir actividades y experiencias previas de vacunación proactiva (visitas con la posibilidad de vacunación "in situ") para acercar y facilitar la vacunación a la población general, así como el diseño de campañas que involucren de forma proactiva a la población a la que va destinada la vacunación y a los responsables de llevarla a término (Modelo PRECEDE) [67].
- Aumentar la formación sobre vacunas a todos los niveles. Se propone impartir conocimientos acerca de las vacunas desde la etapa educativa (en educación primaria y secundaria), y formar en vacunas, de manera rigurosa y exhaustiva, en aquellos estudios de formación profesional y universitaria que conduzcan a las diferentes profesiones sanitarias. Además, se debe acercar el conocimiento y aumentar la formación en vacunas a la población general para reducir los mitos y creencias erróneas preexistentes.
- Mejorar la transmisión del valor de la vacunación. Generar una cultura de la vacunación como elemento de protección individual y colectiva, para tener mejores coberturas.
- Planificar las campañas de vacunación, mediante la adquisición de dosis disponibles en función de los datos de campañas anteriores. Tener en cuenta a los representantes de los centros de salud dado que conocen la estructura, los medios y la organización de cada centro. Dar flexibilidad en la distribución de vacunas según el momento de la campaña. Habilitar una plataforma dinámica y operativa.

Tabla 1 Resumen de las medidas para aumentar las coberturas vacunales.

Investigar

- Estudiar los colectivos que han aumentado su tasa de vacunación y conocer sus motivaciones para vacunarse.
- Explorar el impacto de la infección del virus de la gripe en personas con enfermedades cardiorrespiratorias en nuestro país en términos de morbimortalidad y de consumo de recursos sanitarios.
- Profundizar en el conocimiento y en la búsqueda de vacunas más seguras y efectivas

Informar

- Acercar y difundir los resultados para que resulten más comprensibles y eliminar mitos y creencias acerca de las vacunas.

Formar

- Reforzar el conocimiento sobre vacunas en la población general y en concreto en los colectivos más susceptibles.
- Incluir formación rigurosa sobre vacunas en las profesiones sociosanitarias

Concienciar

- Aplicar estrategias en las campañas de prevención de gripe como las usadas por la DGT, para que la población general sea consciente del riesgo y el impacto que provoca la infección por virus de la gripe.

Implementar

- Fomentar la buena práctica profesional sanitaria, protegiendo a los pacientes y liderando con el ejemplo.

Medidas centradas en las personas con patología cardiorrespiratoria previa

- Investigar y profundizar en el conocimiento sobre el impacto de la infección del virus de la gripe en estas patologías, realizando en este país estudios sobre mortalidad y morbilidad (hospitalizaciones, ingresos en UCI) asociadas a la infección por gripe en esta población con enfermedades crónicas. Por otro lado, se debe difundir la información de los resultados y de los efectos conocidos de la infección del virus de la gripe en este grupo poblacional a través de los medios de comunicación, asociaciones de pacientes y profesionales sanitarios, especialmente por parte de los médicos y profesionales en enfermería de los centros de AP, así como los facultativos especialistas en las áreas de cardiología, neumología, endocrinología y nefrología, entre otros.
- Promover una mayor implicación y un mayor fomento en la indicación de la vacuna a los pacientes por parte de los médicos. Cuando los pacientes acudan a sus consulta o revisiones, se debe indicar la vacunación antigripal en el informe al alta o tras un episodio de hospitalización, como una recomendación más de cuidados y medida de promoción de la salud. La evidencia clínica señala que la recomendación del sanitario es la medida más eficaz para

el incremento de la cobertura vacunal en las personas con patologías previas [68].

Medidas centradas en los grupos prioritarios

- Seguir profundizando en el conocimiento de la inmunosenescencia para la búsqueda de vacunas más seguras y efectivas en los mayores de 65 años. Difundir la información sobre la vacuna de alta dosis y sobre su utilización podría ayudar a mejorar las coberturas. Pueden ser las vacunas de futuro para esta población, ya que buscan una eficacia superior a la de las vacunas conocidas hasta ahora y presentan un perfil de seguridad adecuado.
- Acercar a los destinatarios el mensaje acerca de las vacunas disponibles, explicar y difundir el conocimiento sobre los mecanismos de la inmunidad asociados al envejecimiento adecuando el mensaje a los receptores, e indicando el uso de una vacuna de alta dosis con un perfil de seguridad adecuado.
- En el colectivo de los profesionales sanitarios, ahondar en las causas de las reticencias ante la vacunación o los motivos de vacunarse mediante la realización de encuestas, con el fin de encontrar qué alicientes podrían estimular a población para incrementar su cobertura vacunal.
- "Liderar con el ejemplo", visibilizando la vacunación por parte de este colectivo a través de fotos y mostrando resultados mediante la elaboración de materiales informativos.
- Emplear o realizar formación para rebatir los falsos mitos y creencias, teniendo en cuenta que son profesiones ligadas estrechamente a la ciencia
- Plantear por parte de la Administración Sanitaria la obligatoriedad de vacunación en especialidades y colectivos que por su estrecho contacto con los pacientes puedan ser vectores de transmisión.
- Realizar una vacunación activa por parte de los servicios de Medicina Preventiva/Salud Laboral y enfermería para vacunar al personal sanitario de los diferentes centros. Además, sería interesante incentivar la vacunación mediante beneficios.
- Fomentar la buena práctica profesional sanitaria, protegiendo a los pacientes de desarrollar la infección por gripe y sus complicaciones asociadas para evitar el mayor daño posible.

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CONFLICTOS DE INTERESES

CVP ha participado como ponente o asistente en actividades formativas patrocinadas por Sanofi-Pasteur, GSK, Pfizer y Roche. **VDC** ha participado como ponente en actividades relacionadas con vacunas de Sanofi-Pasteur, GSK, Pfizer o Seqirus. **IRC** ha colaborado en actividades docentes subvencionadas por GSK, MSD, Pfizer y Sanofi Pasteur; como investigadora en ensayos clínicos de vacunas de Ablynx, Abbot, Cubist, GSK, Janssen, Medimmune, Merck, MSD, Novavax, Novartis, Pfizer, Roche, Regeneron, Sanofi Pasteur, Seqirus y Wyeth, y como consultora en Advisory Board de MSD, Pfizer y Sanofi Pasteur. **LAO** ha colaborado en actividades docentes subvencionadas por laboratorios Lundbeck, Almirall, Servier, Esteve, Astra Zeneca, GSK, MSD, Pfizer, Sanofi Pasteur, Lilly, Mylan, Grunenthal y como consultor en Advisory Board de Lundbeck y Pfizer. **JJGO** codirige un curso Universitario de especialización en Vacunas que cuenta con financiación de Sanofi Pasteur y ha participado como ponente y asistido a reuniones científicas sobre vacunas apoyadas por laboratorios Sanofi Pasteur, GSK, y Seqirus. **MTPR** declara no tener conflictos de intereses.

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Review

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Lessons from COVID-19 for future disasters: an opinion paper

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ABSTRACT

A "Pandemic/Disaster Law" is needed to condense and organize the current dispersed and multiple legislation. The State must exercise a single power and command appropriate to each situation, with national validity. The production of plans for the use of land and real estate as potential centers for health care, shelter or refuge is recommended. There should be specific disaster plans at least for Primary Health Care, Hospitals and Socio-sanitary Centers. The guarantee of the maintenance of communication and supply routes is essential, as well as the guarantee of the autochthonous production of basic goods. The pandemic has highlighted the need to redefine the training plans for physicians who, in their different specialties, have to undertake reforms that allow a more versatile and transversal training. National research must have plans to be able to respond quickly to questions posed by the various crises, using all the nation's resources and in particular, all the data and capabilities of the health sector. Contingency plans must consider ethical aspects, and meet the needs of patients and families with a humanized approach. In circumstances of catastrophe, conflicts increase and require a bioethical response that allows the best decisions to be made, with the utmost respect for people's values. Rapid, efficient and truthful communication systems must be contained in a special project for this sector in critic circumstances. Finally, we believe that the creation of National Coordination Centers for major disasters and Public Health can contribute to better face the crises of the future.

Keywords: COVID-19, SARS-CoV2, catastrophes, pandemics, primary care, hospital care, socio-health centers, health organization, teaching in medicine, medical education, specialist training, research, communication, health industry, media, bioethics

Lecciones de la COVID-19 para futuras catástrofes: un documento de opinión

RESUMEN

Es necesaria una "Ley de Pandemias/catástrofes" que condense y ordene la dispersa y múltiple legislación actual. El Estado tiene que ejercer un poder y mando único adecuado a cada situación, con vigencia nacional. Se recomienda la confección de planes de utilización de suelo e inmuebles como centros potenciales de asistencia sanitaria, refugio o albergue. Deberán existir planes de catástrofes específicos al menos para la Atención Primaria, Atención Hospitalaria y Centros Sociosanitarios. La garantía del mantenimiento de las vías de comunicación y abastecimiento es esencial, así como la garantía de producción autóctona de materias de primera necesidad. La pandemia ha puesto de manifiesto la necesidad de redefinir los planes de formación de los médicos que en sus distintas especialidades tienen que asumir reformas que permitan un entrenamiento más versátil y transversal. La investigación nacional debe tener planes para poder responder con rapidez a preguntas que planteen las distintas crisis, utilizando para ello,

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todos los recursos de la nación y en particular todos los datos y capacidades del sector sanitario. Los planes de contingencia deben considerar los aspectos éticos, y cubrir las necesidades de pacientes y familias con un enfoque humanizado. En circunstancias de catástrofe aumentan los conflictos que requieren una respuesta bioética que permita tomar las mejores decisiones, con el máximo respeto a los valores de las personas. La comunicación, rápida, eficiente y veraz debe estar contenida en un proyecto especial para este sector en circunstancias de crisis. Pensamos finalmente que la creación de un Centro coordinador nacional de grandes catástrofes y Salud Pública puede contribuir a enfrentarnos mejor a las crisis del futuro.

Palabras clave: COVID-19, SARS-CoV2, catástrofes, pandemias, atención primaria, atención hospitalaria, centros socio-sanitarios, organización sanitaria, docencia en medicina, educación médica, formación de especialistas, investigación, comunicación, industria sanitaria, medios de comunicación, bioética.

INTRODUCTION

The major concern of the society in general, and of the scientific society in particular, is to predict the future of the COVID-19 pandemic. It is necessary to try to anticipate whether there will be new waves of the disease, whether particularly virulent variants may appear, whether vaccines will evolve at a sufficient rate to cope with the situation and whether the pharmaceutical industry will be able to continue producing effective drugs against present and future coronaviruses.

In addition to the above, lessons need to be drawn from the situation suffered to deal with other potential catastrophes, not only of a viral or microbial nature, but of any other cause.

The COVID Committee of the Illustrious College of Physicians of Madrid, whose mission is to deliberate on this and other aspects related to the pandemic and emerging pathogens, has formulated a series of questions that do not pretend neither to cover the universe of the problem nor to issue any dogma. We have simply intended to offer some reflections to our members, and to whom they may be useful, on lessons for the future learned from COVID-19. The questions have been formulated and discussed by the members of the Committee and the deliberations are set out below.

WHAT LINKS AND PLANS SHOULD BE IMPLEMENTED IN THE EVENT OF MAJOR DISASTERS?

In addition to natural biological threats, which are always latent [1], there are other types of threats, which are current and highly probable.

Spain and the rest of the states, have a response capacity, health and social, that translated into written rules, overwhelms in thousands of pages. But if they are to become real practices, it will be necessary to generate a more synthetic document with freer and more executive decisions, which will allow legally constituted institutions to act effectively among the autonomous, national and constitutional legal tangle and the most elementary natural law [2]. In the early stages of the current pandemic, even with accredited health systems, as fortunately ours is, the response to basic demands (an oxygen supply, a medical visit...), were not always met, or arrived late. The delay, if it could be shortened, was due to the voluntarism, intuition and professionalism of healthcare workers and other social agents, rather than to the established institutional response.

This first line of action of security forces and social and health care, whose raison d'être is immediate intervention, should be strengthened by the State with human and technical resources. An example of what is needed should be plans for the use of land and real estate, which can be made available within hours, to be used as shelters or as areas for assistance or isolation.

Prevention, information and education for the health of the population are essential aspects. Educational programs should be established to promote compliance with hygiene standards and to raise awareness of the usefulness of vaccination and other preventive measures. It is also important to promote self-care and individual responsibility in health.

In major disaster situations, it is essential to secure communication routes, the transport network and the production of essential materials.

The use of social networks and other means of communication allows immediate interconnectivity, which can facilitate rapid and effective organization. Their good use can be decisive in the development of events [3-8].

The transport network is essential for the management of a major disaster and ensuring it will depend on the coordination of a single command, with the involvement, when necessary, of the so-called essential bodies. All available resources must be used, whether by land, sea or air, in order to supply food, equipment, transport of people, etc.

Another line of work that COVID-19 has reminded us of is the necessary and permanent connection of assistance with basic research and with the industrial and productive resources. The initial regulations during the pandemic, far from strengthening them, annulled them. The laboratories of universities and large research centers, which would have had great potential for diagnostic assistance and technological treatment, were preventively closed. International markets with high international demand were resorted to in a situation of low competitiveness, instead of activating and facilitating national production [9, 10]. In addition, in Spain, a national coordination center should be established to facilitate a single management in these circumstances. This has been hindered by the decentralization of healthcare competencies to the autonomous communities.

The national pharmaceutical industry, although with exemplary examples, should ensure sufficient production capacity for essential drugs, especially antimicrobials and vaccines.

A more centralized collaboration and organization in which equity is ensured is necessary. Our nation must not for-

get past experiences and must legislate a law on catastrophes and pandemics that will provide a legal framework for action and collaboration between the public and private sectors. If this is not done, a new opportunity will have been lost and the improvements that can be derived from past experience will not become evident.

In the following points of the document, more specific aspects of the healthcare response are raised that may be of great use in putting an end to this threat or facing the next one, which, as we well know, awaits us.

WHAT ESSENTIAL ELEMENTS SHOULD A MAJOR DISASTER PLAN ADDRESS IN PRIMARY CARE?

In order to face future health emergencies with greater guarantees, it is essential to strengthen Primary Care (PC). The proper functioning of PC guarantees a higher quality, safer, more equitable and efficient healthcare system. The strengthening of PC requires a substantial increase in its financing. Investment in PC should increase from 11% of the current health budget to the 25% recommended by the World Health Organization (WHO) [11]. Investment should cover both human and technological resources and the adequacy of infrastructures.

It is necessary to design in advance a specific contingency plan in PC for major disasters, with the active participation of PC physicians in its elaboration.

In addition to care for the victims of the catastrophic episode, it is essential to ensure access to PC for the rest of the population, particularly the most vulnerable (elderly, chronic, dependent, etc.) [12]. To this end, new alternative care models to the conventional ones should be promoted and consolidated, encompassed in the concept of telemedicine [13] with possibilities of active follow-up of patients with remote monitoring that can guarantee efficient care, control and prevention of chronic processes and multi-pathological patients.

The plan we suggest should promote home care from PC, especially by nurses, providing them with the capacity to provide resources related to the care and attention of complex chronic patients.

It would also increase efficiency and accessibility in PC, the elimination of all those activities that provide little care value and increase bureaucratization, such as the management of sick leave, favoring the digitization of administrative processes [14].

New care models should be implemented with multidisciplinary teams, less dependent on the figure of the family physician, and it is necessary to reorganize the responsibilities of all the professionals that make up PC based on different profiles that allow a more efficient response to demand. It is also necessary to promote the creation and adaptation of new professional profiles (psychologists, occupational therapists, community agents or managers, health promoters, clinical assistants).

Finally, we believe it is important to design and develop internal and external communication plans to ensure the dissemination among professionals of the clinical information generated by healthcare organizations.

HOW SHOULD MAJOR DISASTER PLANS BE ORGANIZED IN HOSPITALS?

It is essential that hospital disaster preparedness is well organized and incorporated into the routine operation of hospitals [15-21].

In the preparation and management of catastrophes, the concept of the maximum benefit of the greatest number of victims takes precedence over that of the individual, and the order of priority in intervention is not determined solely by the severity of the injuries, but by the possibility of survival [17, 18]. Some documents serve as examples of hospital organization in recent catastrophes such as the COVID-19 pandemic and the 11M terrorist attack in Madrid [19,20].

All hospitals should have organized a Commission responsible for preparing a Disaster Plan in advance, specific to each center and to the situations to which it may be exposed (natural disasters, pandemics, terrorism, chemical or biological weapons, accidents due to radioactive contamination, etc). The Commission will report directly to the hospital manager and may be subdivided into groups, with specific composition and responsibilities, mainly the Permanent Disaster Committee and the Disaster Commission.

The Standing Committee should be made up of the hospital's most responsible operational and organizational bodies: Manager, Medical Director, Director of Nursing, Director of Management (or whoever they delegate), Emergency Coordinator, Head of the IT Service, Communication Service or Office, and the President or Coordinator of the General Committee. It is essential to have permanent internal and external communication and coordination within and outside the hospital, with other hospitals, health care facilities that attend to patients (primary care, rescue services, out-of-hospital emergencies, etc.) and the relevant authorities.

The Disaster Plan is made up of those protocols, procedures and pre-established actions to be applied in the management of disasters, seeking the greatest efficiency of the available resources and the least impact on the hospital. The following areas will be represented: direct assistance areas, assistance support areas, General Services, Admission Service, Security Service, Communication Service and Press Office, Information Technology Service, Human Resources Services and Family Care Area.

With regard to organization and operation, it is important to work in advance on:

1.- Defining, forecasting and availability of additional resources needed in the first moments (care spaces, mobilization of human and material resources to the emergency and critical areas that receive the maximum influx of patients).
2.- Defining the essential active activity of the hospital during the disaster, as well as the temporarily delayable one.

3.- To prioritize the safety and support of the workers involved in the attention to the catastrophe.

4.- To ensure updated and truthful information on the evolution of the disaster.

5.- To anticipate and guarantee the management of new needs (protection measures, food, medicines, furniture, etc.).

6.- To establish the means of social and health support for patients and families.

7.- To develop training and support plans in the resolution and decision making of ethical problems [19, 21].

8.- To prepare psychological support groups for patients and workers, dependent on mental health services.

9.- To design stabilization and evacuation plans for pediatric patients in hospitals without a pediatric service.

10.- To have a plan for the reorganization and recovery of the hospital's previous activity, to be applied once the catastrophe is over.

WHAT REFORMS ARE NEEDED IN HEALTH CARE INSTITUTIONS?

In Spain there are more than 400,000 residential places in these socio-health centers for all population groups, with the elderly being the most notable [22]. Residents have pluripathology, need for polypharmacy and have high levels of physical and mental dependence that determine important family and psychosocial conditioning [23].

This situation is reflected in the figures produced by the pandemic with an 80% mortality rate due to COVID-19 in the over-70 age group, reaching up to 47% of deaths in nursing homes [24], figures that could be even higher [25].

The Pandemic has revealed, among others, the following deficits in the socio-health environment, which a future disaster plan should try to solve:

- Significant lack of health personnel assigned from primary care or hospital referral. Doctors and nurses in these centers do not always have the necessary training in family and community medicine or geriatric medicine. In addition, they tend to have a very rapid turnover.

There are usually no plans for catastrophes or pandemics in the social and health centers, nor a plan of audits to guarantee their implementation.

- There are usually no coordinated information systems that facilitate access to residents' medical records for healthcare professionals in order to provide coordinated and speed care.

In view of the above, there is a need to redesign and consolidate a social and health care structure that responds to the needs of these people and these centers, which should include the following:

1- The figure of a liaison Geriatrician in each hospital.

2.- The creation of Residential Care Units by means of multidisciplinary teams of doctors, nurses and pharmacists, depending on primary care, directly coordinated with Hospital Geriatrics and Public Health.

The need for a new regulatory and financing system for the creation of a new model of comprehensive care centered on the person, reducing the fragmentation between social and health care, equalizing the qualifications required as well as the economic compensation [26] (Table 1).

Table 1 **Measures to be contemplated in contingency plans for residential health and social care centers [26]**

1. In relation to the Organization of the residential center itself:
- Location of all residential centers in the area.
- Adjustment of visits according to the incidence of the pandemic.
- Continuous training of all personnel in the different teams.
- Adequate hygiene measures
- Necessary protective equipment
- Isolation capacity in: red zone (infected patients), orange zone (suspected patients) and green zone (not infected and infection overtaken).
2. In relation to the Sociosanitary Coordination:
- Well-established consultation circuits with hospital referents.
- Health and social resources (both human and material) according to the needs of each center and type of patient (degree of dependence).
- Adequate communication with Hospital-PHC-Public Health-SUMMA teams.
- Capacity for diagnostic tests according to indications.

HOW SHOULD THE KNOWLEDGE AND TRAINING OF HEALTHCARE WORKERS BE IMPLEMENTED IN DISASTER PLANS?

The SARS-CoV-2 pandemic has highlighted the main value of the healthcare system, which is its professionals. Especially in the first wave of the pandemic, the need to provide care to an unusual number of COVID 19 patients, which saturated healthcare resources, and the drastic reduction in care for other pathologies, led to substantial changes in the organization of work and healthcare teams [27].

Many healthcare professionals with specialized training had to support teams with high care loads such as the emergency department, hospital wards and critical care areas [28]. Teamwork, motivation and professionalism managed to provide an exceptional response to care, teaching and research needs, even innovating and incorporating technology and digitization in healthcare systems. But it has also had negative consequences not only physically but also emotionally on professionals and sometimes even on care outcomes, by reducing the quality of care in highly specialized environments.

One of the lessons learned from this pandemic leads us to reflect on how the new training models for these healthcare professions should be approached.

The first consideration would be related to the need for competency-based training. Specialized medical training has followed the classic model of programs based on experience acquired in programmed rotations in different care areas with the participation of expert clinical professionals acting as teachers. The evaluation of the results is carried out through the certification of these stays by means of subjective observation and supervised practice, generally without a final exam, which presupposes the benefits of this training model. This model does not ensure homogeneity of results and does not always meet the expectations of professionals. Competency-based training is currently an alternative to these classical training models. They are based on the definition of a series of observable and measurable competencies (knowledge, skills, behaviors and attitudes) that a professional must have in order to meet the needs of patients and solve the problems they pose. The training is based on reflective learning, places the physician in training at the center of the system, incorporates innovative teaching tools such as clinical simulation for the acquisition of competencies, requires the training of teachers as facilitators of this learning, emphasizes periodic and structured formative evaluation with objective and validated instruments through the recording of achievements and sometimes incorporates or facilitates a summative evaluation through certifications that reliably ensure the effectiveness of the training process [29]. All this favors an objective, structured, transparent and effective training process that, promotes autonomous professional development and reduces learning variability [30].

The second, is the need to define what should be the basic competencies for any healthcare professional, regardless of the function he or she performs on a regular basis outside crisis situations. A common and transversal training, beyond the specialization of each program, favors the response in this context. The management of life-threatening emergency situations, the initial response to disasters and especially the acquisition of basic skills such as teamwork and effective communication are essential. Disaster medicine is not incorporated in practically any body of doctrine or in the curricula of the different specialties, although there are clearly defined competencies. During the pandemic, initiatives have been developed that have allowed basic training in critical patient care for many professionals from other areas [31]. This requires innovative teaching methodologies such as clinical simulation to increase the learning curve. There are training programs such as TeamSTEPPS® [32] or crisis management training (CRM) [33] aimed at training leadership, effective communication, supportive behavior, emotional intelligence and other competencies that favor teamwork and flexibility of professionals in situations of uncertainty.

Interdisciplinary training favors collaborative practice, training teams to work together, and has been shown to improve care outcomes. All this requires profound changes in undergraduate and specialized training programs that respond to these needs and ensure the maintenance of competencies through continuing education [34]. Knowing the institutional contingency plans, and their periodic training through drills, is one of the basic pillars to act effectively and safely in these contexts [35].

Other competencies, such as digital competencies and competencies in the use of technology should be considered in the training programs of healthcare professions [36,37].

The best prepared organizations will be the ones that have those professionals with excellence in the specialized technical part but also have the flexibility to adapt to a changing context such as the one we have faced during this pandemic.

WHAT CHANGES IN THE ORGANIZATION OF HEALTHCARE MANAGEMENT ARE MOST NEEDED TO DEVELOP AND ACTIVATE SUCH PLANS?

The COVID-19 pandemic has led to multiple changes and adaptations in health system care and management. Some of these changes could be maintained in the future to improve health care and improve response to emerging situations and are as follows:

1.- There is a need to redesign hospitals to allow for the expansion of critical areas in an agile manner and the isolation of infectious-contagious patients. Hospital contingency plans should foresee where these critical areas should grow, the material needed to equip them and the human resources that should be employed.

2.- Work in coordination between the three levels of care (primary care, out-of-hospital emergencies and specialized hospital medicine) to be able to carry out common preventive medicine. The management of at least the most frequent processes between the different levels of care should be promoted by means of agreed and common protocols and clinical pathways. The use of information systems as tools to help the professional and not only as a way of recording and storing clinical and administrative information on the patient is fundamental to their success.

3.- To increase the coordination of the different national territories, so that solutions to common problems are shared, patients' healthcare information is available when they are treated outside their Autonomous Community and to ensure the greatest possible equity in healthcare, regardless of where it is provided.

4.- The crisis situation led to the need to urgently hire multiple health care workers and even to incorporate medical personnel who were not yet specialized or who had already retired. The organizational staffs of health centers should be adequately equipped to respond to crisis emergencies and would make it possible to avoid or mitigate the suspension of surgical, diagnostic or chronic patient care activity in the event of any emergency, as has occurred in the current crisis.

5.- The multidisciplinary work carried out in the COVID-19 care has highlighted the value of this type of strategy, which

provides the knowledge of various specialists in the care of the same care process. Previous experience in this regard already existed, but the organization of the system according to processes with multidisciplinary groups should be encouraged, especially in prevalent processes affecting the elderly population with comorbidities, where optimal clinical management should be integrated and not patched according to the specialist who is evaluating the patient at a given moment.

6.- Teleconsultation has been greatly enhanced during the pandemic. The key to its success, however, does not lie in generalizing it, but in choosing appropriately the patients who can benefit from it, avoiding unnecessary trips to the health center if it is not going to add value to the care provided. The first contact with the health system when faced with a health problem should always be face-to-face, so that the physician can carry out an adequate anamnesis and physical examination, which is imperative at the first moment.

7.- A double care circuit should be maintained in emergency departments for the location of patients with communicable respiratory diseases to avoid secondary contagion with other patients and ensure adequate protection of healthcare personnel. This measure can be useful in other common respiratory viruses such as influenza or RSV pandemics, in addition to the coronavirus pandemic.

8.- Health education and patient empowerment from the initial stages of education is essential to prevent the general population from consulting for minor problems that distort the care of patients who do require such care.

WHAT ERRORS IN THE COMMUNICATION POLICY SHOULD BE CHANGED IN THE FUTURE?

The analysis of the information received by the population during the SARS-CoV-2 pandemic reflects three fundamental problems: the excess of information in general, the confusion caused by the diversity of official sources, and the enormous amount of biased or false information that has been disseminated. At the very least, these three problems should be corrected in future disaster plans.

Information overload, without going into its quality, has led to the coining of the term infoxication [38], and can have negative consequences on prevention behaviors [39]. It can also be the cause of neuropsychiatric disorders (gathered in the information overload syndrome) with diverse presentations, almost all related to anxiety pictures, loss of concentration and even social isolation responses [40]. In an environment of press freedom, with multiple sources of information and the added participation of social networks, it is difficult to propose measures to correct this overload. Health education of the population and the leadership of the health authorities could allow sufficient and contrasted information, avoiding the need to resort to multiple sources.

The diversity of official national and international sources has generated information that is not only excessive, but sometimes confusing, contradictory or openly erroneous. Without falling into the ridicule of the declarations of the presidents of some nations, examples include those relating to the use of masks at the beginning of the pandemic, the appropriate meters to maintain social distance or the number of people who could gather in each territory or period [41]. The dispersion of measures of the European Union states and the Spanish autonomous communities has multiplied the dissemination of heterogeneous information, which has overloaded the population and undermined their confidence. It seems essential that, for the future, there should be real leadership by the World Health Organization (WHO) and adequate coordination of the health and information policies of the European Union and Spain, using single, homogeneous channels.

Beyond the excess, there has been an enormous amount of biased or false information that the WHO has called "infodemic" [42]. The United Nations (UN) has described it as something as worrying as the pandemic itself, as it can generate dangerous health behaviors, distrust towards the media and health authorities, social or racial discrimination and even violence.

Given the fundamental role of social networks in the dispersion of false and biased news [43], solutions have been proposed such as public health organizations taking a leading role in the networks, both disseminating truthful information and combating hoaxes [44]. The social networks themselves have taken measures to reduce disinformation [45], and the activity of many groups of journalists to safeguard the veracity of information should be highlighted. An example of this is Web Newsguard (https://www.newsguardtech.com). It has even proposed the use of artificial intelligence systems to detect and stop hoaxes and rumors at an early stage [46].

Although the right to freedom of expression and information must always be taken into account, the right to health and the obligation to provide truthful and verifiable information must also be considered. In addition to internal control measures by social networks and control by information professionals, a large part of the solution to this problem involves training society in the critical use of information technologies [41,43,44] and paying attention to the doubts and fears of the population, in order to provide them with appropriate answers [42].

IS THERE A NEED FOR NATIONAL RESEARCH COORDINATION TO ADDRESS THE QUESTIONS THAT NEW DISEASES OR NEW SITUATIONS MAY PRESENT?

Although the impact experienced during the first wave has given rise to pessimistic reflections on the real potential of our national health system research, the fact is that it has also highlighted the organizational capacity and care efforts of the professionals and their research efforts. Spain occupies the 7th place in the ranking of research publications related to COVID, which is undoubtedly a good ranking [47].

In Spain, public research in biomedicine is mainly car-

ried out in hospitals and universities, on numerous occasions through research institutes that enable collaboration between the two. The Instituto de Salud Carlos III (ISCIII), is the ultimate responsible for public biomedical research in Spain, with a dual functional dependence on the Ministry of Science and Innovation and the Ministry of Health [48,49]. The structure of the ISCII for the promotion and development of Research is well established through its own or linked national research centers (CNI), in addition to other networks and consortium centers (CIBERs, RETICs, Platforms).

In March 2020, at the beginning of the pandemic, and immediately after the declaration of the state of alarm, the ISCIII opened a research fund of 24 million euros and, in fact, in that year 129 projects were approved, of which only 17 corresponded to initiatives of CIBERs or national Centers and Platforms. These projects have already been the subject of some publications [50,51], as have been published the results of the ENE study, directly developed by the ISCIII, [52] or the COMBIVAC study, also directly funded by the ISCIII and with the participation of its researchers [53].

Applied research is crucial in pandemic situations. With the very high number of cases available, the informatic tools and the current research structures, an adequate national research strategy would allow, without adding new organisms, to have viral biology data or, where appropriate, the pathogen involved in the pandemic that, together with the epidemiological data, could be applied to prevention policies, generate knowledge quickly applicable to the detection of vulnerable populations and to research in therapeutic responses supporting care recommendations. This without forgetting basic research for the development of vaccines and new pharmacological molecules.

Without detriment to the research initiatives of the different groups, in an eventual National Pandemic Plan, biomedical research should be included and centralized under the direction of the ISCIII with an action plan that could very well follow these lines.

- Appoint an independent Scientific Advisory Board, made up of professionals with recognized knowledge and experience in the areas related to the problem generating the crisis.
- Establish the National Centers, Networks and Platforms that should work in a coordinated manner in the planning of research projects.
- Identify priority research areas according to needs and feasibility.
- Allocate available resources on a preferential basis for the development of national projects that have been established.
- Establish alliances with "bigdata" technology companies that can streamline the processing of clinical records.
- Establish research alliances with the pharmaceutical and medical technology industry.

WHAT ASPECTS OF HUMANIZATION AND ETHICS NEED TO BE IMPROVED IN THE FACE OF A POTENTIAL CATASTROPHE IN THE FUTURE?

Many and varied are the ethical conflicts that have arisen during the pandemic and have been addressed according to its evolution. Suffice it to mention the different reports of the Spanish Bioethics Committee [54-56], etc. that have helped to deal with the complex situations experienced in the different waves. Learning from this pandemic must be used to safely face new scenarios.

In the future, it will be necessary to bring bioethics closer to daily clinical practice, relying on bioethicists and the different bioethics advisory bodies at all levels (institutional, hospital care, etc.). During the pandemic, many scientific societies, faced with the new challenges, drew up recommendations on ethical aspects that were of great help in decision-making. Local initiatives should be avoided, trying to unify ethical principles and their implementation in an agile and continuous way in order "...not to leave ethics aside, but rather, in a crisis situation, it is even more important to articulate ethical guidelines for extraordinary circumstances that help decision-makers under pressure...". [57].

It is necessary to establish consensual criteria for prioritizing the allocation of resources in situations where there is an imbalance between the demand for care and the available resources. In these cases, decision-making is highly complex and requires appropriate management of resources without undermining the rights and dignity of citizens.

The different ethical reports [54-59] establish that triage (admission to ICU, transfer to hospital from residential centers, etc.) requires the maximum expansion of resources, and must be guided by clinical criteria that, objectively, although in the context of uncertainty, help in decision making. [60]. Protocols should include flexible criteria and be adapted to each particular situation. To this end, the best recommended strategy is the creation of care teams that update these protocols and that, in crisis situations, are responsible for the daily assessment of incoming and outgoing patient flows. In this regard, a basic element is to encourage society to plan care in advance on the basis of its values and preferences, especially in the most vulnerable population.

Once the above is well defined, it will be possible to determine the criteria for resource allocation in a critical disaster situation, recommending mixed model criteria that include utility, equity, and protection from vulnerability. However, it will not always be possible to fully achieve both utility and equity and there will be no single right way to solve the problems. But what is important is that the decisions that are made are made in a transparent process that takes into account local circumstances along with those of the rest of the autonomous communities and the country [60].

It is also necessary to consider the needs of humanization in the assistance and aspects related to the families. The compulsory isolation of infected persons adds to the seri-

ousness of the disease, an affective deprivation, both in the family and in health, never experienced before. The need for a "more compassionate environment" has been learned. [60, 61], with a fundamental rule: no person should die alone without having his or her physical, psychological, emotional, and spiritual needs effectively met. Therefore, in the face of any catastrophe, in the 21st century, it will always be necessary to articulate and guarantee the necessary measures so that all patients have the opportunity to live their end of life accompanied and cared for by the healthcare team in their palliative needs. Along these lines, particularly fragile patients such as children, the disabled, the mentally ill, the elderly in need of help with activities of daily living, etc. must always be able to be accompanied. With today's means (video-calls, telematic connections, etc.), situations of isolation such as those that have been experienced are no longer understandable, and all hospital units should provide the means for face-to-face contact (limited in time) and telematic contact (the time required by the patient). All these measures, as well as triage, should be taken by multidisciplinary teams at middle management level that can guarantee these measures of "compassionate environment as a superior act of hospital humanization" to the different ward teams on a daily basis [61]. Finally, communication with families at this point should be considered a priority and should be as frequent as possible, communicating in an empathetic and sensitive way to the adequacy of care according to the changing clinical situation.

A legal framework according to the clinical-ethical situations in disaster situations will be necessary. Usually after the pandemic subsides, claims and lawsuits begin. In a pandemic, professionals face a different praxis scenario than usual, acting in a way that is conditioned by limited resources. In this pandemic, initiatives have been taken by legal associations expressing the possibility of expressly excluding healthcare professionals from their claims, without excluding the viability of claims against those responsible for the hypothetical damage caused in their case. Therefore, as demanded by numerous national and international scientific societies, with what has been learned in the COVID, it is necessary the existence of legal systems that protect professionals from legal liability taking into account the context in which the care activity is developed in a disaster situation.

IS THERE A NEED FOR A NEW NATIONAL COORDINATION CENTER FOR MAJOR DISASTERS?

The response to large-scale disasters is usually coordinated from the Office of the President of the Government, to facilitate the participation of the different Ministerial Departments. This has been the case in the current COVID-19 pandemic. However, for the preparation and response to new pandemics, there is a certain social agreement on the need to strengthen public health structures. Without prejudice to the fact that this includes especially the public health services of the Autonomous Communities, since they have the main competences in this field, there is a broad parliamentary consensus on the need to strengthen public health structures. [62] and major public health societies [63], that this can be achieved through the creation of a State Center for Public Health, already contemplated in the General Public Health Law 33/2011. For this reason, the Ministry of Health has budgeted for the development of this center, which would become operational during the current legislature. The creation of this State Public Health Institution is described in component 18 of the Government of Spain's 2021 Recovery, Transformation and Resilience Plan. [64], which indicates that it should be configured as a center of excellence that performs functions in two main areas: public health surveillance, risk assessments and analysis of the health situation of the Spanish population; and, preparation and coordination of the health system in the face of public health threats, mainly of an epidemic nature, but also other health crises resulting from, for example, climate change (increased temperatures, floods, etc.). It should also monitor and evaluate the Public Health Strategy, and contribute technical and scientific capabilities to the design and evaluation of health policies and to the improvement of public health services and their actions [63,64].

Probably, the best legal form for the new institution, in accordance with the legal context and the functions envisaged, is that of an "agency", since it can exercise administrative powers and is characterized by autonomy, agility and flexibility in management, transparency, accountability and evaluation by results. In particular, a State Agency for Public Health (AESP) attached to the Ministry of Health, through the Secretariat of State for Health, can assume direct management powers [63].

We are awaiting the regulatory development of this institution and its creation and development. The adequate provision of material and human resources, the use of appropriate working procedures, and its relative independence from political power are necessary conditions for it to be an effective instrument for improving Spain's response to new public health challenges in the coming years. Experience will tell if all this is possible.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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A systematic literature review and expert consensus on risk factors associated to infection progression in adult patients with respiratory tract or rectal colonisation by carbapenem-resistant Gram-negative bacteria

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ABSTRACT

Objective. Risk factors (RFs) associated with infection progression in patients already colonised by carbapenem-resistant Gram-negative bacteria (CRGNB) have been addressed in few and disperse works. The aim of this study is to identify the relevant RFs associated to infection progression in patients with respiratory tract or rectal colonisation.

Material and methods. A systematic literature review was developed to identify RFs associated with infection progression in patients with CRGNB respiratory tract or rectal colonisation. Identified RFs were then evaluated and discussed by the expert panel to identify those that are relevant according to the evidence and expert's experience.

Results. A total of 8 articles were included for the CRGNB respiratory tract colonisation and 21 for CRGNB rectal colonisation, identifying 19 RFs associated with pneumonia development and 44 RFs associated with infection progression, respectively. After discussion, the experts agreed on 13 RFs to be associated with pneumonia development after respiratory tract CRGNB colonisation and 33 RFs to be associated with infection progression after rectal CRGNB colonisation. Respiratory tract and rectal colonisation, previous stay in the ICU and longer stay in the ICU were classified as relevant RF independently of the pathogen and site of colonisation. Previous exposure to antibiotic therapy or previous carbapenem use were also common relevant RF for patients with CRGNB respiratory tract and rectal colonisation.

Conclusion. The results of this study may contribute to the early identification of CRGNB colonized patients at higher risk of infection development, favouring time-to-effective therapy and improving health outcomes.

Keywords: Risk factor; Multi-drug resistance; Carbapenem-resistant gram-negative bacteria; colonization; expert consensus.

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Revisión sistemática de la literatura y consenso de expertos sobre los factores de riesgo asociados a la progresión de la infección en pacientes adultos con colonización del tracto respiratorio o rectal por bacterias gramnegativas resistentes a carbapenémicos

Objetivo. Los factores de riesgo (FR) asociados a la progresión de la infección en pacientes ya colonizados por bacterias gramnegativas resistentes a carbapenémicos (BGNRC) han sido abordados en pocos y dispersos trabajos. El objetivo de este estudio es identificar los factores de riesgo relevantes asociados a la progresión de la infección en pacientes con colonización del tracto respiratorio o rectal.

Material y métodos. Se realizó una revisión sistemática de la literatura para identificar los FR asociados a la progresión

de la infección en pacientes con colonización del tracto respiratorio o rectal por BGNRC. Los FR identificados fueron luego evaluados y discutidos por el panel de expertos para identificar aquellos que son relevantes según la evidencia disponible y la experiencia de los expertos.

Resultados. Un total de 8 artículos fueron incluidos en el análisis de los FR en la colonización del tracto respiratorio y 21 para la colonización rectal, identificándose 19 FR asociados al desarrollo de neumonía y 44 FR asociados a la progresión de la infección respectivamente. Tras la sesión de discusión, los expertos acordaron que 13 FR se asociaban al desarrollo de neumonía tras la colonización del tracto respiratorio por BGNRC y 33 FR a la progresión de la infección tras la colonización rectal por BGNRC. La colonización del tracto respiratorio y rectal, la estancia previa en la UCI y una estancia prolongada en la UCI se clasificaron como FR relevantes independientemente del patógeno y del lugar de colonización. La exposición previa a antibióticos o el uso previo de carbapenémicos se clasificaron como FR relevantes para varios de los patógenos tanto en pacientes con colonización del tracto respiratorio como rectal.

Conclusión. Los resultados de este estudio pueden contribuir a la identificación precoz de los pacientes colonizados por BGNRC con mayor riesgo de desarrollo de infección, favoreciendo el uso temprano de terapias efectivas y mejorar los resultados en salud de estos pacientes.

Palabras clave: factor de riesgo, multirresistencia, bacterias gramnegativas resistentes a carbapenémicos; colonización; documento de consenso.

INTRODUCTION

Multidrug-resistant (MDR) bacteria have become a relevant and urgent public health threat because few effective antibiotics are available for the treatment of infections caused by these bacteria. Among MDR pathogens, Gram-negative bacteria require special attention because of their resistance to carbapenems, the most active and potent agents available against MDR Gram-negative pathogens [1,2]. In 2017, the World Health Organisation published the list of priority pathogens for which innovative treatments are urgently needed. Carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacterales* are listed as the most critical pathogens [3]. In Spain, recently published studies show that carbapenem-resistant Gram-negative bacteria (CRGNB) are the cause of a high number of infections [4–6]. More specifically, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacterales* (including *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae)* were the most common bacteria [4–6].

In most cases, these pathogens may colonize one or more patients' sites, constituting a silent and dangerous reservoir that can lead to the spread of these bacteria and a risk of development of associated clinical infections that may lead to clinical complications, including patient's death [7,8]. CRGNB colonisation prevalence has been studied on different populations (e.g., patients undergoing organ transplants, general population, ICU patients) and is estimated to occur in 4% to 57% of the patients [9–12]. CRGNB may settle in different sites such as urinary tract, skin, or abdominal cavity. Among them, rectal and respiratory tract colonisation are of especial attention due to their high prevalence and the most common sites of screening with microbiological tests [13–15]. CRGNB, concretely *P. aeruginosa*, *A. baumannii* and *Enterobacterales*, have been identified as common rectal and respiratory tract colonizers [11,12].

In the last years, it has been suggested that colonisation is associated with clinical infection development and its potential consequences (e.g., septic shock) [7]. Risk factors (RFs) associated with CRGNB infection or colonisation have been widely studied [16–19]. Recently, an expert's consensus study performed in Spain has been published to help to clarify the RFs associated with CRGNB *P. aeruginosa* and *A. baumannii* infection development [20]. Factors associated with a risk for infection progression in already CRGNB colonised patients have been addressed in few and disperse works. Due to the lack of information and uncertainty regarding the RFs associated with infection progression from CRGNB rectal or respiratory tract colonisation, the main objective of this study is to provide clinical recommendations from an experts's consensus based on the current available evidence.

MATERIAL AND METHODS

Study design. The study was designed in four different phases: **1)** Systematic literature review (SLR) to identify RFs associated to infection development after rectal or respiratory tract colonisation; **2)** Creation of the expert panel; **3)** Development of a questionnaire to evaluate identified RFs in SLR and **4)** Results analysis and consensus session.

PHASE I: Systematic Literature Review

A SLR was conducted in October 2021 to identify the evidence available on RFs associated to clinical infection after respiratory tract (Site 1) and rectal (Site 2) CRGNB colonisation. The pathogens included for each site were *P. aeruginosa*, *A. baumannii,* and *Enterobacterales*, more specifically *Klebsiella pneumoniae* and *Escherichia coli*. The sources of information were biomedical databases such as MEDLINE, Cochrane Library and MEDES. The search strategy is depicted in Figure 1. Inclusion and exclusion criteria for each of the sites are described in Table 1 and Table 2. The population of study were adults for rectal colonisation, while for respiratory tract colonisation it was limited to adults in the ICU with mechanical ventilation. MeSH terms used for each site and pathogen are described in Supplementary Table 1.

PHASE 2: Expert panel

A multidisciplinary panel consisting of 2 coordinators (an infectiologist and an intensivist) and 8 experts (2 intensivists, 3 infectiologists and 3 microbiologists) was created to review the RFs identified in the SLR and evaluate them for

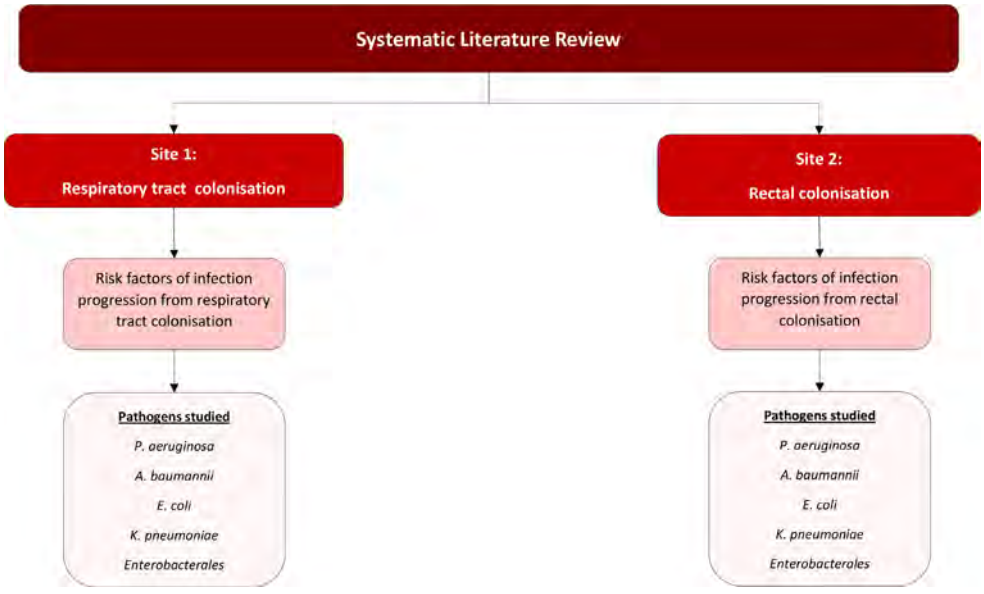

Figure 1 Systematic Literature Review search strategy

Table 1 Inclusion and exclusion criteria for respiratory tract colonisation SLR studies

Site 1: Respiratory colonisation	
Inclusion criteria	Exclusion criteria
Articles including patients with respiratory colonisation caused by carbapenem-resistant Gram-negative bacteria, especially *P. aeruginosa*, *A. baumannii*, *Enterobacterales* (*E. coli*, *K. pneumoniae*). **Works published in the last 5 years** (2016-2021) Publications in English or Spanish **Population:** Adults (≥ 18 years), **ICU inpatients with artificial airway**	One-arm or pre-post studies. Studies from low- and middle-income countries. Articles related with genetics Articles including "COVID", "COVID-19", "coronavirus" or "SARS-CoV-2" infections Articles focused on base pathologies other than CRGNB infection (e.g., cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease) Paediatric population studies

Table 2 Inclusion and exclusion criteria for rectal colonisation SLR studies

Site 2: Rectal colonisation	
Inclusion criteria	Exclusion criteria
Articles including patients with rectal colonisation caused by carbapenem-resistant Gram-negative bacteria focused on *P. aeruginosa*, *A. baumannii*, Enterobacterales (*E. coli*, *K. pneumoniae*). Works published in the last 5 years (2016-2021) Publications in English or Spanish **Population:** Adults (≥18 years).	One-arm or pre-post studies Studies from low- and middle-income countries. Articles related with genetics Articles including "COVID", "COVID-19", "coronavirus" or "SARS-CoV-2" infections Paediatric population studies

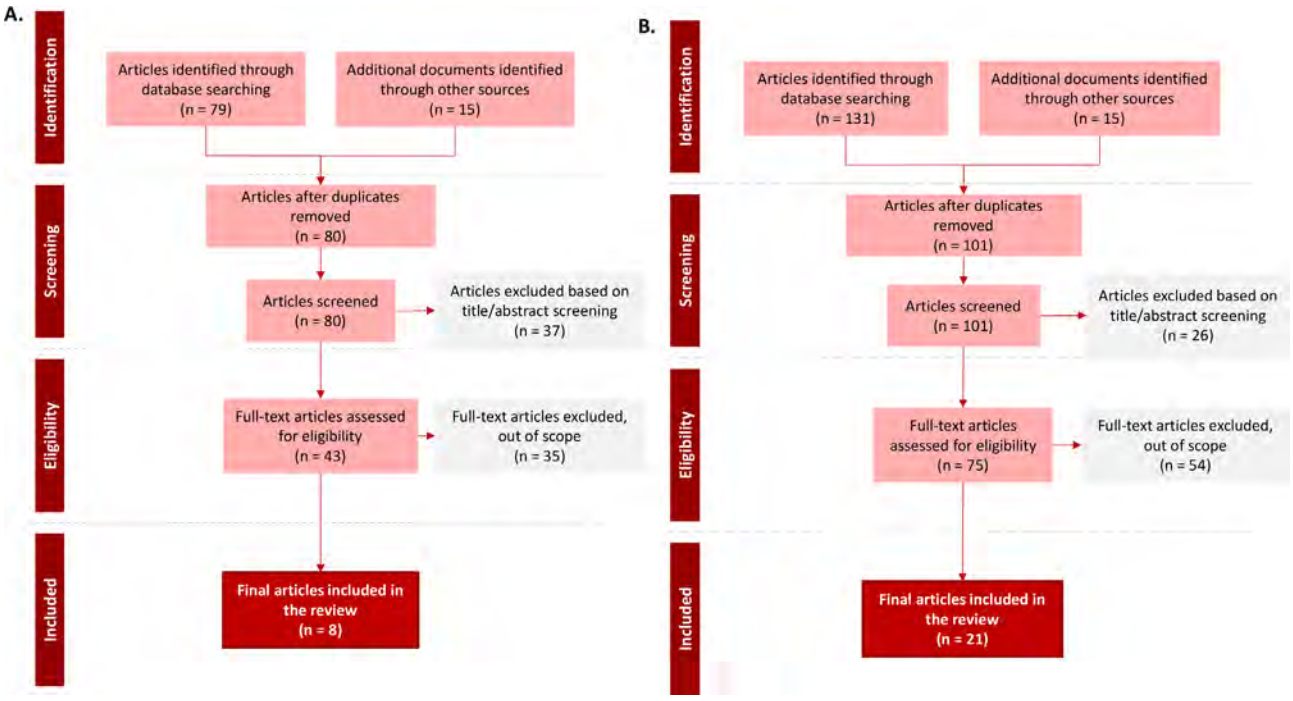

Figure 2 | **PRISM diagram of literature review results for A. Respiratory tract CRGNB colonization and B. rectal CRGNB colonization.**

its relevance based on available information and their own clinical experience. The Spanish experts were chosen based on their clinical experience in the study area, as well on their participation in similar studies published in indexed journals.

PHASE 3: Development of materials to evaluate each of the RF identified in the SLR

For each article included in the SLR, a file was created to collect information in a systematic way. Information included for each article was: site of colonisation, pathogen, reference, year of publication, country, study design, setting, ward, inclusion criteria and exclusion criteria, total number of patients in the study and for each study group, type of statistical analysis and a summary of results of the univariate and multivariate analysis.

Together with the articles file, a questionnaire for each of the sites (respiratory tract and rectal colonisation) was developed to evaluate each of the RF by the expert panel. The questionnaire included all RF associated with infection development after CRGNB colonisation identified in the SLR. The questionnaire was then divided in two parts. **1) Evidence based**, which included RFs by pathogen associated with infection progression in colonised patients found in the SLR and presented for each pathogen. For each pathogen, two differentiated sections were assessed; RF commonly associated to infection progression and pathogen-specific RF. 2) **Expert's opinion**, which included RF commonly associated to infection progression after CRGNB colonisation but were not found in the SLR for a specific pathogen. Each RF was presented as a statement to assess its relevance, and a 3-point scale was used to evaluate it "1-I agree with the statement"; "2- I moderately agree with the statement" and "3- I disagree with the statement". Experts were asked to provide their rational to their answer.

PHASE 4 Results analysis and consensus session

The questionnaire and article files were sent to the experts. Experts were asked to evaluate the relevance of each RF related to infection progression after CRGNB colonisation based on the evidence available and their own clinical experience. In case there was no evidence, or they had no clinical experience, experts were asked to provide their expert opinion.

Results of the RF assessment were included in an excel database and were presented as a percentage of experts that answered each of the options. An arbitrary cut-off of 80% (8 out of 10) was set to determine agreement among the experts for each of the answers. The criteria agreed to include RF as relevant were: **1)** Acceptance of RFs with a score ≥80% with score "1- I agree" or "2 - I moderately agree". In case of a score ≥80% on the item "3- I disagree", the RF was excluded from the study. **2)** For those RF with <80% on any of the 3 scale items, those with ≥80% agreement when pooling "1- I agree " and "2- I moderately agree" were included as relevant. **3)** Those RF with <80% agreement after pooling "1- I agree " and "2- I moderately agree" were discussed during the consensus session. **4)** If

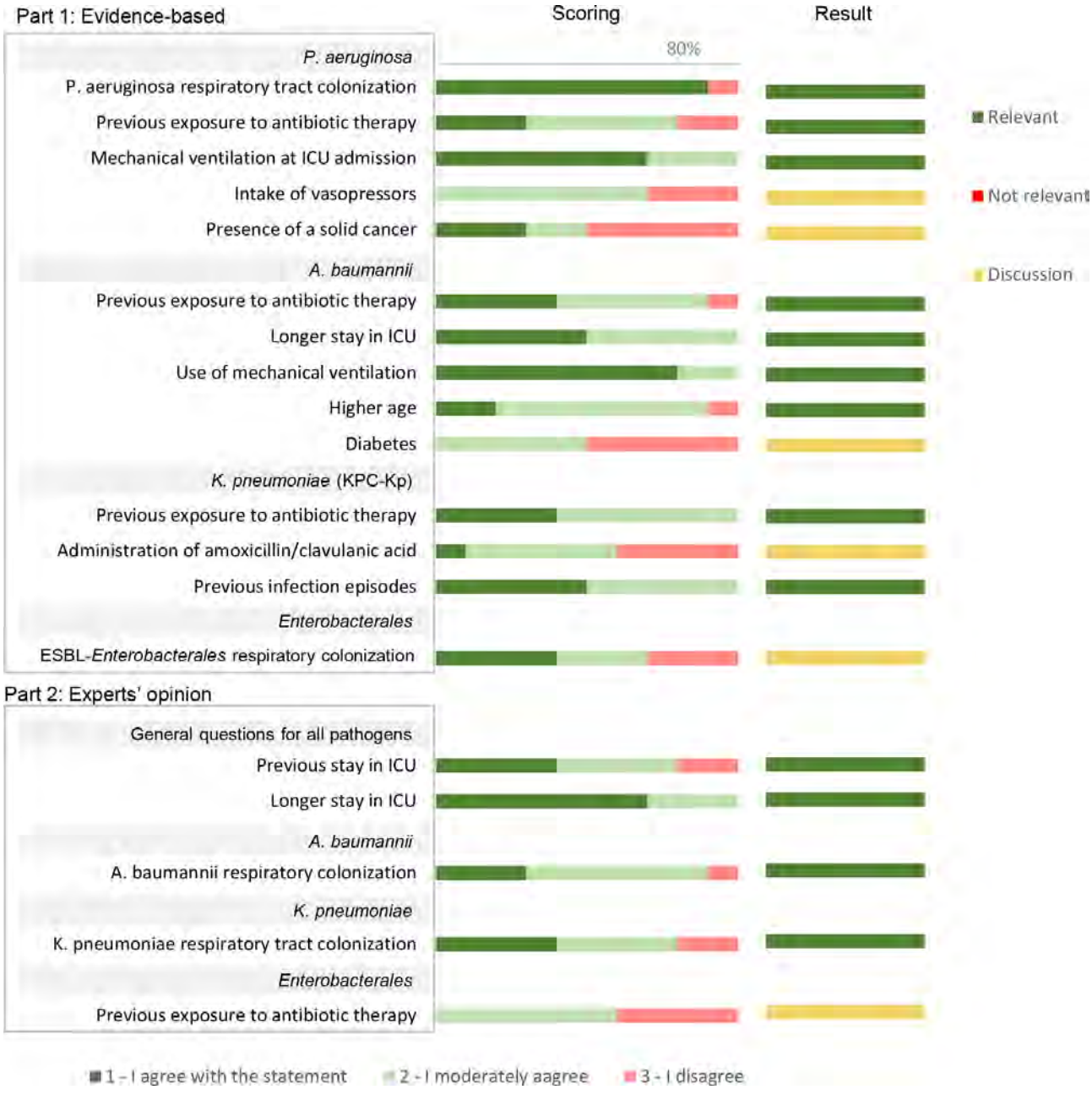

Figure 3 **Scoring and results of the assessment of risk factors associated with pneumonia progression after CRGNB respiratory tract colonization in ICU adult inpatients with mechanical ventilation. Scores are represented according to the percentage of responses on the 1- I agree, 2-moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, not relevant, or needed to be discussed in the consensus session.**

additional information or clarification was provided during the discussion session that changed the interpretation of the RF, the scoring could be reassessed and classified according to the above criteria. **5)** The experts were able to exclude from the study those RFs that they considered ambiguous and difficult to interpret.

An online consensus session was performed in January 2022 to present the results and discuss the RF that did not reach consensus. For each RF to be discussed, a bar chart with the percentage of responses and a summary of statistical analysis of the studies where those RF were identified were presented. Finally, the RFs were accepted or excluded based on the previously described criteria.

Figure 4A | **Scoring and results of the assessment of risk factors identified in the literature associated with infection progression after CRGNB rectal colonization in adult population. Scores are represented according to the percentage of responses on the 1- I agree, 2-moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, excluded, or discussed in the consensus session.**

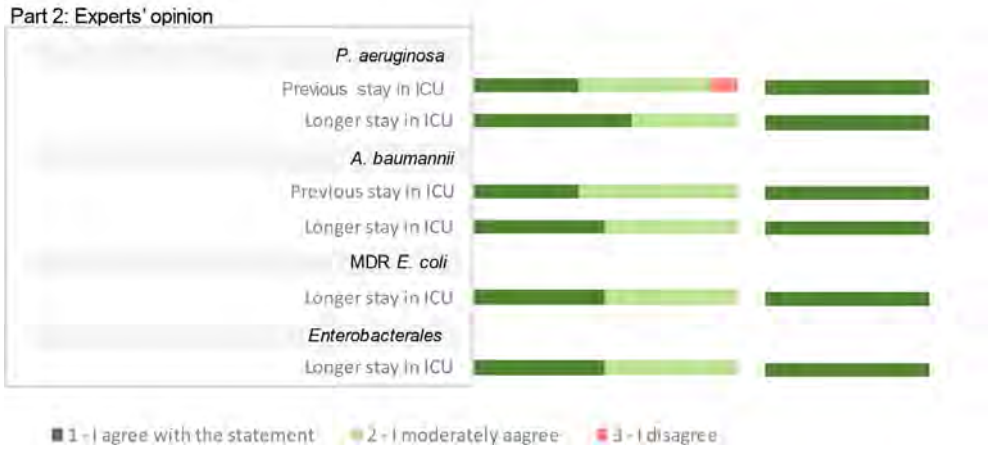

Figure 4B **Scoring and results of the assessment of risk factors associated with infection progression after CRGNB rectal colonization in adult population according to expert's opinion. Scores are represented according to the percentage of responses on the 1- I agree, 2-moderately agree and 3- do not agree. Result column shows if the risk factor was included as relevant, excluded, or discussed in the consensus session.**

RESULTS

Systematic Literature Review (SLR). A total of 80 articles were identified in the SLR for the respiratory tract CRGNB colonisation site, and 8 articles were finally included. For rectal CRGNB colonisation site, a total of 101 were identified and 21 included in the review. PRISM diagrams of SLR results are included in Figure 2.

Results analysis. A total of 19 RF associated with pneumonia progression after respiratory tract CRGNB colonisation were identified and evaluated for its relevance by the expert panel. Out of 19 RF identified, 13 of them were included as relevant RF according to the agreed criteria, and 6 of them were discussed in the consensus session (Figure 3). Out of the 13 included as relevant, "respiratory tract colonisation" by *P. aeruginosa*, and "use of mechanical ventilation" in patients colonised by *A. baumannii* reached ≥80% in the score "1- I agree with the statement".

Regarding the rectal colonisation site, a total of 44 RF were identified to be associated with infection progression and evaluated for its relevance by the expert panel. Out of 44 RF identified, 27 of them were included as relevant RF according to the agreed criteria and 17 of them were discussed in the consensus session (Figure 4A and B). Out of the 27 included as relevant, "rectal colonisation" by *A. baumannii* and "longer stay in ICU" in patients colonised by *K. pneumoniae* reached ≥80% in the score "1- I agree with the statement". "Peptic ulcer" in patients with *Enterobacterales* colonisation also reach ≥80% in the score "2- I moderately agree with the statement".

Consensus session. The results from the questionnaire were presented to the expert panel for each of the sites (respiratory tract and rectal colonisation). According to the stablished criteria, RFs that did not reach consensus in the previous exercise were presented for discussion.

Results after discussion and re-evaluation of RF associated with pneumonia development after respiratory tract colonisation in adult ICU inpatients with mechanical ventilation are described in Figure 5.

In the respiratory tract RF discussion, the panel agreed to include "ESBL-*Enterobacterales* respiratory colonisation" as a relevant RF for pneumonia development. On the other hand, experts reached consensus on excluding as relevant the following RFs for pneumonia development: "intake of vasopressors" and the "presence of solid cancer" in patients colonised with *P. aeruginosa*; "Diabetes" in patients colonised with *A. baumannii*; "administration of amoxicillin/clavulanic acid" in patients colonised with carbapenemase-producing *K pneumoniae*; "previous exposure to antibiotic therapy" in patients colonised with *Enterobacterales*.

The "intake of vasopressors" or "presence of solid cancer" were discarded by the experts due to study design of the evidence provided, which proved association but not causality [21,22]. In addition, the presence of solid cancer is a broad concept that should be nuanced (e.g. site, stage, immunocompromised status of the patient), as well the confusion factors associated, such us the treatment the patient receives [22]. Similar rational was concluded when discussing "diabetes" as a RF. The study analysed the risk of infection recurrence and not infection progression, besides the fact that uncontrolled diabetes or patients' general condition would be more relevant factors than the presence of diabetes itself [23]. The RF "administration of amoxicillin/clavulanic acid" was excluded because even though there is a strong association according to the literature, it is not associated to an increased risk [24]. "Previous exposure to antibiotic therapy" in patients

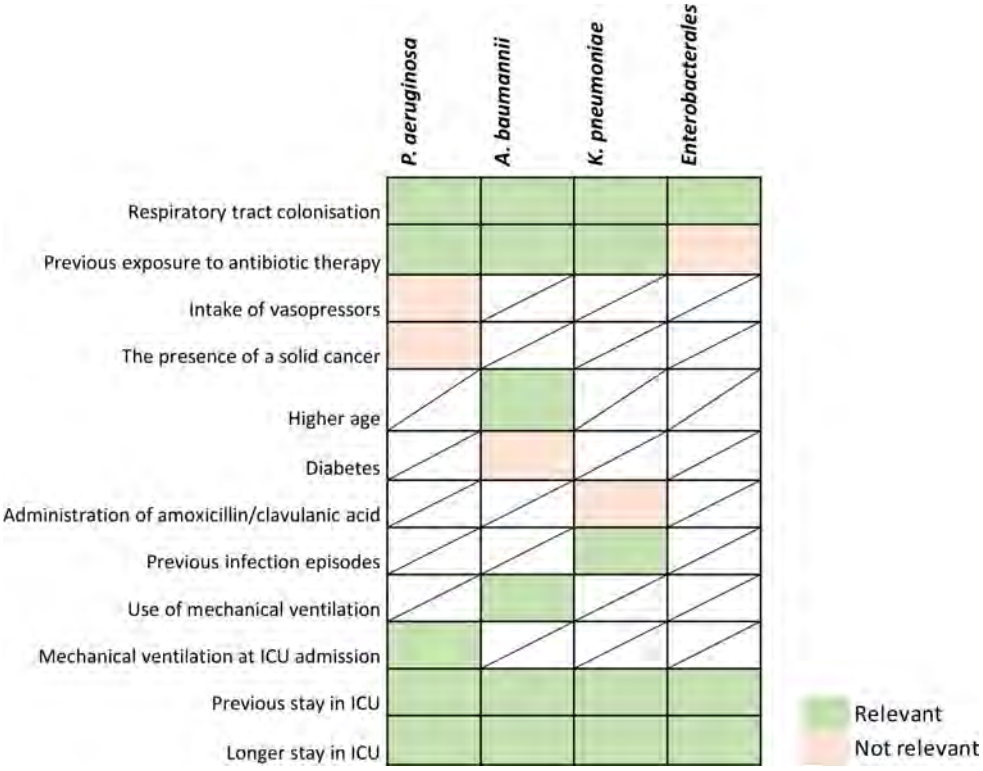

Figure 5 **Results after consensus of risk factors classified according to its relevance by pathogen in pneumonia progression after CRGNB respiratory tract colonisation in ICU adult inpatients with mechanical ventilation.**

colonised with *Enterobacterales* was excluded being this RF associated to pathogen resistance development rather than pneumonia development.

Results after discussion and re-evaluation of RF associated with infection after rectal colonisation in adult patients are described in Figure 6.

During the rectal RF discussion, out of 17 RF included in the discussion**,** the expert panel agreed to include 5 of the 17 discussed RF as relevant for infection development in rectal colonised patients: "*P. aeruginosa* rectal colonisation"; "ESBL *E. coli* rectal colonisation"; "Presenting a high-level resistance to carbapenems", "previous stay in ICU" and "use of mechanical ventilation" in patients with MDR *Enterobacterales* rectal colonisation. Consensus was not reached for the RF "Liver dysfunction" in patients colonised with *A. baumannii*, as approximately half of the experts considered it relevant due to the significant association proved in literature, while the other half considered that the disease description was too broad, lacking important information about the disease such as the grade or patient status.

On the other hand, the expert panel agreed on considering not relevant for infection development the following RFs: "Active exposure to antibiotic therapy" in *P. aeruginosa* rectal colonised patients; "previous cephamycin use" and "previous cephalosporin use" in A. baumannii colonised patients; "administration of amoxicillin/clavulanic acid" and "Transfer between hospital units" in patients with MDR *K. pneumoniae* rectal colonisation; "Congestive heart failure", "Chronic obstructive pulmonary disease (COPD)", "Immunological disorder", "Diabetes", "urological disorder" and "psychiatric disorder" in patients with MDR *Enterobacterales* rectal colonisation.

The rationale behind excluding "Active exposure to antibiotic therapy" in patients colonised by *P. aeruginosa* was the same as in the respiratory tract site, being this RF associated to pathogen resistance development rather than pneumonia development [25]. "Previous cephamycin use", "previous cephalosporin use" and "administration of amoxicillin/clavulanic acid" were excluded because even though there is a strong association according to the literature, it is not associated to an increased risk [24,26]. "Transfer between hospital units" was excluded as that would depend on the units implicated (e.g., chronic vs. acute) [27]. "Congestive heart failure", "Chronic obstructive pulmonary disease (COPD)", "Immunological disorder", "Diabetes", "Urological disorder" and "Psychiatric disorder" were excluded as relevant RFs by the expert panel due to lack of significant association [10,28]. Furthermore, associated factors to these comorbidities such us disease stage, treatment received, or patient status could be relevant factors to be considered.

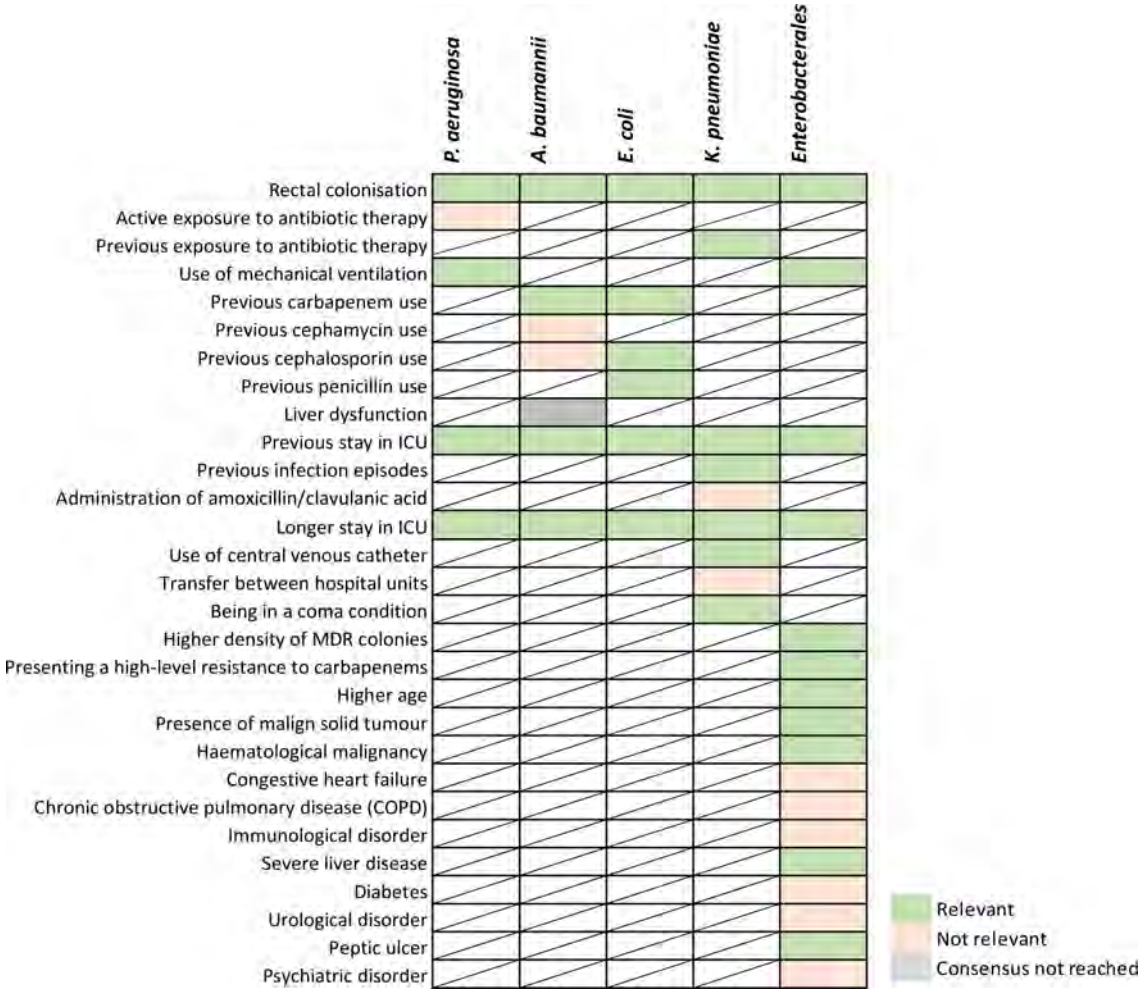

Figure 6 **Results after consensus of risk factors classified according to its relevance by pathogen in infection progression after CRGNB rectal colonisation in adult patients.**

The evidence supporting each of the RFs identified in the SLR after consensus session are described in the Supplementary Table 2 and Supplementary Table 3.

DISCUSSION

CRGNB colonisation constitute a silent and dangerous reservoir that can lead to the spread of these bacteria, in addition to the associated risk of developing clinical infections [7,8]. Identification of RFs associated with infection development in CRGNB colonised patients is important to assist physicians in identifying those patients at high risk that would require close monitoring or/and administration of early treatment. Nevertheless, few studies have been published analysing RFs associated with infection progression in CRGNB colonised patients.

In this study, a total of 181 articles were identified in the SLR, 80 for the respiratory tract site and 101 for rectal site. Of these, 8 articles were finally included in the CRGNB respiratory tract colonisation and 21 for CRGNB rectal colonisation, identifying 19 RFs associated with pneumonia development and 44 RFs associated with infection progression, respectively. Most of RFs identified were supported by literature (74% of RF from the respiratory tract site and 86% of RF from rectal tract), and few were considered based on expert's experience and opinion (Supplementary Table 2 and Supplementary Table 3).

After discussion, the experts agreed on 13 RFs to be associated with pneumonia development after respiratory tract CRGNB colonisation and 33 RFs to be associated with infection progression after rectal CRGNB colonisation (Table 3). Consensus was not reached for the RF "Liver dysfunction" in patients colonised with *A. baumannii* in the rectal tract.

Noteworthy, respiratory tract and rectal colonisation,

Table 3 **Risk factors associated to infection development in adult patients with CRGNB colonisation by site and pathogen.**

	Risk factor associated with pneumonia development in patients with CRGNB respiratory tract colonisation admitted in the ICU and receiving artificial airway	Risk factor associated with the development of infections in patients with CRGNB rectal colonisation
P. aeruginosa	*P. aeruginosa* respiratory tract colonisation [22] Previous exposure to antibiotic therapy [21,22] Mechanical ventilation at ICU admission [29] Previous stay in ICU Long stay in the ICU	*P. aeruginosa* rectal tract colonisation [30] Use of mechanical ventilation [29] Previous stay in ICU Long stay in the ICU
A. baumannii	*A. baumannii* respiratory tract colonisation Previous exposure to antibiotic therapy [31] Higher age [31] Use of mechanical ventilation [31] Previous stay in ICU Long stay in the ICU [31]	*A. baumannii* rectal tract colonisation [26] Previous carbapenem use [26] Previous stay in ICU Long stay in the ICU
E. coli	N/A	*E. coli* rectal tract colonisation Previous carbapenem use [32] Previous cephalosporin use [32] Previous penicillin use [32] Previous stay in ICU [32] Long stay in the ICU
K. pneumoniae	*K. pneumoniae* respiratory tract colonisation Previous exposure to antibiotic therapy [24] Previous infection episodes [24] Previous stay in ICU Long stay in the ICU	*K. pneumoniae* rectal tract colonisation [10] Previous exposure to antibiotic therapy [24] Previous stay in ICU [33,34] Previous infection episodes [24,34] Longer stay in ICU [27] Use of central venous catheter [27,33] Being in a coma condition [33]
Enterobacterales	*Enterobacterales* respiratory tract colonisation [35] Previous stay in ICU Long stay in the ICU	*Enterobacterales* rectal tract colonisation [28,35–37] Use of Mechanical ventilation [38] Previous stay in ICU [39] Long stay in the ICU Higher density of MDR colonies [35] Presenting a high-level resistance to carbapenems [36] Higher age [10] Presence of malign solid tumour [10,28] Haematological malignancy [10] Severe liver disease [28] Peptic ulcer [28]

previous stay in the ICU and longer stay in the ICU were classified as relevant RFs independently of the pathogen and site of colonisation. Previous exposure to antibiotic therapy or previous carbapenem use was also a common relevant RF for patients with CRGNB respiratory tract and rectal colonisation, supported by the literature and experts' opinion, showing altogether their relevance when identifying patients at high risk of infection development after CRGNB colonisation in those sites.

Other RFs identified are also consistent across the sites, for instance "use of mechanical ventilation", "previous infection episodes", "higher age", or "pre-existing comorbidities", nevertheless the association is pathogen specific for each of the sites. The experts agreed that pre-existing comorbidities could be a relevant RF to identify patients at high-risk of infection development, nevertheless, those should be refined based on disease severity and patient status. Interestingly, some of the relevant RF associated to infection progression in this study have been associated with CRGNB infections in hospitalized patients in several studies, such as prior use of antibiotics, prior hospital or ICU stay and

length of stay [16–18].

The RFs that were excluded by the expert panel were generally due to the lack of significant association with increased risk in the literature, or because the study design was inadequate to answer the study question. In some cases, RF were excluded due to the existence of confounding factors that might be more relevant that the identified RFs themselves.

The limitations of this study are first, the low number of studies identified, due to the scarce evidence available, with most of the RFs identified being supported by only one study. Secondly, the design of the studies identified in the SLR, with different inclusion and exclusion criteria among them. Further prospective studies with less variability between patient populations would be needed, which would also make meta-analysis studies possible. For those reasons, the involvement of an expert panel with extensive experience in the field strengthens the study results.

To our knowledge, this study provides the best evidence available based on SLR and experts' opinion of the RFs associated with infection development in CRGNB colonised patients. The results of the study may contribute to the early identification of colonized patients at higher risk of infection development, favouring time-to-effective therapy and improving health outcomes.

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CONFLICTS OF INTEREST

RF has participated as a speaker or consultant for MSD, Pfizer, Shionogi, Gilead, Grifols and Menarini. **AS** has participated in advisory meetings or as a speaker in educational activities for Pfizer, MSD, Angelini, Gilead Sciences and Shionogi. **RC** has participated in education activities organised by MSD, Pfizer and Shionogi and worked on research projects funded by MSD, Shionogi and Venatrox. **JLP** has participated in education activities and advisory meetings organised by Novartis, MSD, Pfizer and Gilead, Angelini and Shionogi and worked on research projects funded by Novartis. **CG-V** has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly, Shionogi as well as a grant from Gilead Science, Pfizer and MSD. **JG-M** has participated as a speaker in educational activities for MSD, Pfizer and Shionogi. **NL** has participated in advisory meetings or as a speaker in educational activities funded by Pfizer, MSD, Menarini and Shionogi. **PR** has participated as consultant and speaker in educational activities organized by Pizer, MSD, Menarini and Shionogi. **MS** has collaborated in training or research projects and taken part in symposia, meetings or consultancies organised or funded by Gilead, MSD, Janssen, Pfizer and Shionogi. **VP** has participated in accredit ed educational activities sponsored by MSD, Pfizer and Shionogi and has been a consultant for Pfizer, Shionogi and Correvio. **AG-P** and **XB** are employees of Omakase Consulting S.L. that received funding from Shionogi Inc. to develop and conduct this study.

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Impacto de la bacteriemia por *Staphylococcus aureus* en pacientes con COVID-19

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RESUMEN

Introducción. La enfermedad causada por SARS-CoV-2 (COVID-19) ha supuesto un desafío para los profesionales sanitarios desde su aparición. *Staphylococcus aureus* es uno de los principales patógenos causantes de infecciones bacterianas en pandemias virales. Sin embargo, se debe estudiar bien la co-infección por *S. aureus* causante de bacteriemia en pacientes con COVID-19.

Métodos. Se analizaron los casos de bacteriemia por *S. aureus* (BSA) atendidos en el Hospital Miguel Servet (Zaragoza) desde marzo de 2020 hasta febrero de 2021. Se compararon las características clínicas, los factores de riesgo y mortalidad de los pacientes con BSA asociada a COVID-19 respecto los pacientes no-COVID-19.

Resultados. Se identificaron 95 pacientes con BSA. El 27,3% fueron COVID-19 positivos. La BSA representó el 9,9% de las bacteriemias, siendo el segundo microorganismo en frecuencia tras *E. coli*. La bacteriemia nosocomial fue más frecuente en el grupo de pacientes con COVID-19. La fuente de BSA fue desconocida en el 46,2% de los pacientes con COVID-19. La fuente de BSA más frecuente en estos pacientes fue la respiratoria (26,9% vs 0%; P<0,001) seguida de la cutánea (15,5% vs 15,9%; P=1). El desarrollo de sepsis fue más frecuente en los pacientes con COVID-19 (61,5% vs 7,8%; P=0,336) y de ellos, los que recibieron dosis de dexametasona >6 mg/día (62,5% vs 37,5%; P< 0,05).

Conclusiones. Nuestros datos sugieren que la BSA influye negativamente en la evolución de los pacientes con COVID-19. Sin embargo, se requieren más estudios y preferiblemente prospectivos para obtener datos sólidos sobre el impacto de la BSA en los pacientes con coronavirus.

Palabras clave: bacteriemia; *Staphylococcus aureus*; COVID-19; mortalidad;

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Impact of *Staphylococcus aureus* bacteremia in COVID-19 patients

Introduction. The disease caused by SARS-CoV-2 (COVID-19) has been a challenge for healthcare professionals since its appearance. *Staphylococcus aureus* has been described as one of the main pathogens causing bacterial infections in viral pandemics. However, co- infection with *S. aureus* causing bacteremia in patients with COVID-19 has yet to be well studied.

Methods: We performed a e study of S. aureus bacteremia (SAB) at Hospital Miguel Servet (Zaragoza) from March 2020 to February 2021. The clinical characteristics, mortality and risk factors of adults hospitalized patients with BSA associated COVID-19 compared to patients without COVID-19.

Results. A total of 95 patients with SAB were identified. 27.3% were positive for SARS-CoV-2. SAB represented 9.9% of bacteremia, being the second agent in frequency after *E. coli*. Nosocomial bacteremia was more frequent in the group of COVID-19 patients. The most frequent source of BSA in these patients was the respiratory source (26.9% vs 0%; P<0.001) followed by the skin (15.5% vs 15.9%; P=1). The development of sepsis was more frequent in COVID-19 patients (61,5% vs 7,8%; P=0,336) and among them, who received dexamethasone at doses > 6 mg/day (62.5% vs. 37.5%, P<0.05).

Conclusions. Our data suggest that BSA has a negative impact on the evolution of patients with COVID-19. However, further and preferably prospective studies are required to obtain solid data on the impact of BSA on coronavirus patients.

Keywords: bacteremia; *Staphylococcus aureus*; COVID-19; mortality

INTRODUCCIÓN

La enfermedad causada por el SARS-CoV-2 (COVID-19) es una enfermedad infecciosa que se identificó por primera vez en diciembre de 2019 en Wuhan, China, y actualmente es pandémica [1,2]. Esta infección ha supuesto un formidable desafío

médico para los sistemas de salud y los profesionales sanitarios.

Las infecciones bacterianas secundarias asociadas a infecciones virales respiratorias están bien descritas en la literatura y se conoce que son causa de una mayor morbilidad y mortalidad. En concreto, entre los pacientes infectados con el virus de la gripe las bacteriemias se han asociado a una mortalidad cercana al 50% en comparación con el 1,4% en pacientes con gripe sin bacteriemia [3]. Las especies bacterianas principalmente asociadas a infecciones virales son *Mycoplasma pneumoniae, Staphylococcus aureus, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus y Klebsiella* spp [4].

Actualmente se están llevando a cabo estudios epidemiológicos sobre las sobreinfecciones bacterianas en los pacientes con COVID-19, especialmente las bacteriemias [5]. Además, se está observando una creciente incidencia de estas co- infecciones en los pacientes con COVID-19 que han ingresado en las unidades de cuidados intensivos (UCI), así como mayores tasas infección por bacterias nosocomiales multirresistentes, poniendo en relieve la necesidad de prestar especial atención al uso de tratamientos empíricos de amplio espectro en pacientes con COVID-19 [1,6,7].

No obstante, los datos sobre las infecciones bacterianas secundarias en pacientes COVID- 19 son limitados debido a la propagación todavía en curso de esta enfermedad en todo el mundo.

En nuestro medio, la incidencia poblacional de bacteriemia por *S. aureus* (BSA) varía de 10 a 30/100.000 personas -año y continúa siendo un reto diario para los clínicos dada su elevada mortalidad y morbilidad [8,9]. A pesar de los esfuerzos en mejorar el manejo de esta infección, no se ha conseguido observar una mejoría significativa de su pronóstico en los últimos años ya que la población en riesgo continúa aumentando [9].

S. aureus se ha descrito como uno de los principales patógenos causantes de infecciones bacterianas en pandemias virales previas [3]. Sin embargo, todavía se debe estudiar bien la asociación de las co-infecciones por *S. aureus* y los pacientes infectados con SARS-CoV-2, así como su impacto en cuanto a morbilidad y mortalidad para buscar medidas preventivas.

MATERIAL Y MÉTODOS

Temas de estudio y recopilación de datos. Se trata de un estudio observacional y retrospectivo realizado a partir de la revisión de los casos de BSA documentados por hemocultivo y atendidos en el Hospital Miguel Servet de Zaragoza. Se incluyeron pacientes adultos que ingresaron en el hospital entre el 4 de marzo de 2020 (fecha del primer positivo para SARS-CoV-2 en Aragón) hasta el 15 de febrero de 2021.

Datos microbiológicos y clínicos. Para la detección microbiológica, los hemocultivos se incubaron en BD BACTEC ™ FX durante 5 días. La identificación de los hemocultivos positivos se realizó por espectrometría de masas (MALDI-TOF MS) (MaldiBiotyper® Bruker Daltonics). La sensibilidad antibiótica se determinó mediante MicroScan WalkAway (Beckman Coulter) siguiendo los criterios vigentes del European Committee on Antimicrobial Susceptibility Testing (EUCAST).

La detección de RNA viral se realizó por RT-PCR, principalmente con Allplex ™ (Seegen, Corea), COBAS 6800tm (Roche, Suiza) Panther (Hologic, San Diego), Cobas Liat (Roche, EE. UUy Xpert Xpress (Cepheid, Sunnyvale). Los casos se clasificaron en pacientes con COVID-19, aquellos positivos para SARS- CoV-2 por PCR a través de frotis nasofaríngeo, y en pacientes no- COVID-19. Se consideró BSA asociada a COVID-19 en los pacientes que desarrollaron la bacteriemia hasta un mes después de la positividad de la PCR para SARS-CoV-2.

Se analizó la fuente de infección considerándose bacteriemia relacionada con el catéter (BRC) el aislamiento de *S. aureus*, en el hemocultivo extraído tanto de vena periférica como en el cultivo semicuantitativo de la punta del catéter en un paciente, con cuadro clínico de sepsis y sin otro foco aparente de infección. En las situaciones en las que no se enviaron la punta del catéter a cultivar, se consideró BRC cuando se aisló *S. aureus* tiempo diferencial mayor a 120 minutos entre el hemocultivo extraído por el catéter y por venopunción [10]. Para la interpretación de los cultivos de esputo, se comprobó que cumplían los criterios de calidad de Murray y Washington y se consideró *S. aureus* cuando el crecimiento era en cantidad significativa y predominante en el cultivo. En las muestras obtenidas por fibrobroncoscpia los puntos de corte se fijaron en 1.000 ufc/ml para el cultivo del cepillado bronquial y 10.000 ufc/ml para el cultivo bacteriano del lavado broncoalveolar. El foco cutáneo se diagnosticó a partir del aislamiento de *S. aureus* en la muestra obtenida de la lesión (herida).

A partir del Servicio de Admisión y Documentación Clínica y de la historia clínica electrónica de nuestro centro, se obtuvieron datos demográficos (edad y sexo) y clínicos (obesidad, enfermedad renal crónica, HTA, diabetes, dislipemia, neoplasia, broncopatía crónica, trasplante previo, enfermedad hepática y reumática) de los pacientes. Los antimicrobianos recibidos se clasificaron como empíricos (antibiótico pautado antes del aislamiento microbiológico) o dirigido (pautado una vez conocida la identificación bacteriana).

En el grupo de los pacientes con BSA asociada a COVID-19 se recogieron las terapias recibidas, clasificando a los pacientes en aquellos que recibieron dexametasona (DXT) a dosis bajas (d1), 6 mg al día durante 14 días administrada por vía oral o por vía intravenosa, pacientes que recibieron DXT a dosis altas (d2), siendo superiores a 6 mg al día y pacientes que recibieron tratamiento con tocilizumab. También se recogió la necesidad de ingreso en UCI y de ventilación mecánica invasiva (VMI).

Las variables principales empleadas para valorar el impacto de la bacteriemia fueron la mortalidad hospitalaria a los 14 y 30 días del primer hemocultivo positivo, el desarrollo de complicaciones (aortitis, endocarditis, espondilodiscitis, artritis y abscesos), sepsis y bacteriemia persistente, definida por la presencia de hemocultivos positivos a las 72 horas del tratamiento antibiótico adecuado.

Análisis estadístico. Se analizaron las características clí-

Tabla 1 Características demográficas y clínicas

	No COVID-19 n=69 (72,6%)	COVID-19 n=26 (27,3%)	p
Sexo (varón); N (%)	54 (78,3%)	18 (69,2%)	0,517
Edad; Media años, [DE]	70,0 [57,0;81,0]	68,5 [63,2;77,2]	0,858
Obesidad (IMC > 30);N (%)	25 (36,2%)	7 (26,9%)	0,540
ECV; N (%)	35 (50,7%)	11 (42,3%)	0,616
Hipertensión arterial; N (%)	46 (66,7%)	15 (57,7%)	0,566
Diabetes mellitus; N (%)	27 (39,1%)	8 (30,8%)	0,607
Dislipemia; N (%)	26 (37,7%)	15 (57,7%)	0,128
Enfermedad renal crónica; N (%)	19 (27,5%)	8 (30,8%)	0,955
Neoplasia; N (%)	25 (36,2%)	5 (19,2%)	0,180
Broncopatía crónica; N (%)	11 (15,9%)	6 (23,1%)	0,549
Trasplante; N (%)	4 (5,8%)	1 (3,8%)	1,000
Enfermedad hepática; N (%)	9 (13%)	0 (0%)	0,060
Enfermedad reumática; N (%)	5 (7,2%)	2 (7,6%)	1,00

IMC: índice de masa corporal. ECV: enfermedad cardio- vascular (cardiopatía isquémica, insuficiencia cardiaca, accidente cerebro- vascular, accidente isquémico transitorio, etc.).

Tabla 2 Variables asociadas a COVID-19

	No COVID-19 n=69 (72,6%)	COVID-19 n=26 (27,3%)	p
Mediana de días desde el ingreso hasta el primer hemocultivo positivo	1,00 [0,00;6,00]	6,50 [1,25;13,8]	0,012
Unidad de cuidados intensivos	14 (20,3%)	9 (34,6%)	0,236
Ventilación mecánica invasiva	7 (10,1%)	9 (34,6 %)	0,011
Bacteriemia nosocomial	29 (42%)	23 (88,5 %)	< 0,001

nicas de los pacientes con BSA asociada a COVID-19 así como los factores que influyen en el aumento de la mortalidad en este grupo, comparándolo con los pacientes con BSA no asociada a COVID-19 con el objetivo de observar diferencias entre los grupos.

Se realizó un análisis descriptivo de las variables recogidas mediante medidas de tendencia central (media o mediana) (edad, tiempo transcurrido desde el ingreso hasta el primer hemocultivo positivo), y medidas de dispersión (desviación estándar o rango intercuartílico). La comparativa entre grupos se realizó mediante las pruebas de la t de Student o la U de Mann-Whitney para comparar variables continuas de distribución normal y no normal respectivamente. Para comparar proporciones de las variables categóricas, se empleó la prueba de la chi cuadrado con corrección de continuidad o corrección de Yates. Los Odds Ratio (OR) de sufrir un evento de interés se calculó a partir de modelos de regresión logística uni- o multi-variantes, siendo la variable dependiente la ocurrencia/ausencia del evento y la/s variables independientes aquellas que se consideraron de interés. Para calcular la significación de cada coeficiente del modelo se utilizaron el estadístico de Wald. Todos los cálculos estadísticos se realizaron utilizando el software estadístico R versión 4.3.1 y los paquetes apropiados.

Aprobación ética. El Comité de Ética de la Investigación de Aragón (CEICA) aprobó el estudio y consideró la no necesidad de solicitar consentimiento informado para su realización debido a las condiciones de confidencialidad en la recogida de datos y la naturaleza retrospectiva del estudio.

RESULTADOS

Datos microbiológicos, clínicos y tratamiento antibiótico. Se identificaron 95 pacientes en nuestro hospital con diagnóstico de BSA en el periodo establecido. Del total de la muestra, 26 pacientes (27,3%) fueron positivos para SARS-CoV-2 por RT-PCR.

El número de extracciones de hemocultivos realizadas fue de 15930, diagnosticándose bacteriemia en 958 pacientes, siendo la tasa de positividad de los hemocultivos del 12,1%. La BSA representó un 9,9 % de las bacteriemias totales, siendo el segundo agente etiológico de bacteriemia en frecuencia tras *Escherichia coli* que fue el responsable de 297 bacteriemias (31%). La tasa de contaminación de los hemocultivos fue del 5,4% (852 hemocultivos).

El tiempo medio que transcurrió desde que el hemocultivo se incubó hasta que resultó positivo fue de 12 horas, sin diferencia entre los pacientes con COVID-19 y no COVID -19 (p= 0,613). La mayoría de las bacteriemias fueron monomicrobianas (90,6%) y en el caso de las polimicrobianas (9,4%) se asociaron a bacilos Gram negativos el 66,7% de las veces.

Las características clínicas de los pacientes por grupos se muestran en la tabla 1. Las comorbilidades más prevalentes en los casos COVID-19 de nuestra muestra fueron la hipertensión, dislipemia, ECV, diabetes mellitus y la obesidad, sin ser diferentes a las comorbilidades de los pacientes no- COVID-19 con BSA. No se encontraron diferencias estadísticamente significativas entre grupos.

El tratamiento antibiótico empírico fue adecuado en el 61,5% (16/26) de pacientes con infección por coronavirus sin encontrar diferencias estadísticamente significativas respecto a los pacientes no co-infectados (61,5% vs 47,8%; P =0,557).

El antibiótico dirigido **más empleado en el grupo de pacientes** con COVID-19 fue daptomicina (34,6%) seguido de cloxacilina (26,9%). Se empleó biterapia en un 23,1% (6/26) de

Tabla 3 Fuente de bacteriemia por *S. aureus*

	No COVID-19 n=69 (72,6%)	COVID-19 n=26 (27,3%)	p
Fuente desconocida	45 (65,2%)	12 (46,2%)	0,145
Foco catéter venoso central	6 (8,7%)	1 (3,8%)	0,669
Foco urológico	7 (10,1%)	2 (7,6%)	1
Foco respiratorio	0 (0%)	7 (26,9%)	< 0,001
Foco piel y partes blandas	11 (15,9%)	4 (15,4%)	1

los pacientes de este grupo. No se encontraron diferencias estadísticamente significativas en el tratamiento antimicrobiano empleado entre ambos grupos.

La mediana de duración del tratamiento antimicrobiano fue significativamente mayor en el grupo de los pacientes no COVID-19, 19 días [13;30] vs 14 días [4;24] en pacientes con COVID-19 positivos (P= 0,038).

Datos asociados a COVID-19 y tratamiento inmunosupresor. El 34,6% (9/26) de los pacientes con COVID-19 con BSA requirieron ingreso en UCI y VMI, resultando esto último estadísticamente significativo (34,6% vs 10,1%; P < 0,05). La mediana de días desde la fecha de ingreso hasta el primer hemocultivo positivo para *S. aureus* fue mayor en el grupo de los pacientes infectados por coronavirus con una diferencia estadísticamente significativa (6,5 vs 1; P< 0,05). La bacteriemia nosocomial fue significativamente más frecuente en el grupo de pacientes con COVID-19 (Tabla 2).

El 26,9% del grupo COVID-19, recibió pauta d1, el 46,1% recibió pauta d2 y el 23% de los pacientes recibieron tratamiento con tocilizumab. Los que recibieron tratamiento d2 desarrollaron un cuadro de sepsis secundario a la bacteriemia en mayor proporción que los pacientes que no recibieron este tratamiento, resultando estadísticamente significativo (62,5% vs 37,5%, P < 0,05).

Fuente de bacteriemia. La fuente de bacteriemia fue desconocida en el 46,2% de los pacientes con COVID-19. La fuente de infección conocida más frecuente de nuestra muestra fue la piel y las partes blandas (15,8%) sin encontrar diferencias estadísticamente significativas entre pacientes con COVID-19 y no COVID-19. Siete pacientes del total presentaron como fuente de infección la respiratoria, siendo todos ellos pacientes con COVID-19 positivos e ingresados en UCI, resultando estadísticamente significativo (P< 0.001) (Tabla 3).

El 15,4% de los pacientes con COVID-19 presentaron BSA resistente a meticilina (SARM), sin encontrar diferencias estadísticamente significativas respecto a los pacientes no COVID-19 (15,4% vs 15,9%, P=1).

Tabla 4 Mortalidad y complicaciones asociadas a la bacteriemia por *S. aureus*

	No COVID-19 n=69 (72,6%)	COVID-19 n=26 (27,3%)	p
Sepsis	33 (47,8%)	16 (61,5%)	0,336
Bacteriemia persistente	19 (27,5%)	8 (30,7%)	0,783
Espondilodiscitis	7 (10,1%)	1 (3,8%)	0,439
Embolismos periféricos	5 (7,2%)	0 (0%)	0,318
Endocarditis	5 (7,2%)	0 (0%)	0,318
Aortitis	1 (1,4%)	3 (11,5%)	0,061
Abscesos órganos sólidos	2 (2,9%)	0 (0%)	1
Abscesos piel y partes blandas	2 (2,9%)	1 (3,8%)	1
Artritis	5 (7,2%)	1 (3,8%)	1
Mortalidad global	26 (37,6%)	12 (46,1%)	0,222
Mortalidad a los 14 días	15 (21,7%)	8 (30,8%)	0,517
Mortalidad a los 30 días	11 (15,9%)	4 (15,4%)	1

Complicaciones y mortalidad. No se observaron diferencias estadísticamente significativas entre pacientes con COVID-19 y no COVID-19 en el desarrollo de: endocarditis (0% vs 7,2%), espondilodiscitis (3,8% vs 10,1%), embolismos periféricos (0% vs 7,2%), aortitis (11,5% vs 1,4%), abscesos en órganos solidos (0% vs 2,9%), abscesos en piel y partes blandas (3,8% vs 7,2%) ni artritis (3,8% vs 7,2%).

La bacteriemia fue considerada persistente en el 30,7% (8/26) de los pacientes con COVID-19, no encontrándose diferencias estadísticamente significativas respecto a los pacientes no COVID-19 (30,7% vs 27,5%, P= 0,783). El desarrollo de sepsis secundaria a la bacteriemia fue mayor en el grupo de pacientes co-infectados por coronavirus (61,5% vs 47,8%, P= 0.336).

De manera global, no hubo diferencias estadísticamente significativas entre la mortalidad de los pacientes con BSA y COVID-19 respecto a los pacientes no co- infectados por coronavirus (Tabla 4 y Figura 1).

No hubo diferencias en cuanto al desarrollo de complicaciones derivadas de la bacteriemia en función del tratamiento COVID-19 recibido.

La mortalidad de los pacientes que desarrollaron sepsis fue significativamente mayor (91,6% vs 8,3%, P < 0,01).

DISCUSIÓN

Durante el periodo de estudio, en nuestro centro se notificó una tasa global de 0,27% (95/35.174) BSA.

La incidencia de la BSA en nuestro medio varía de 10 a 30/100.000 personas -año [8,9]. En nuestro estudio, el 27,3%

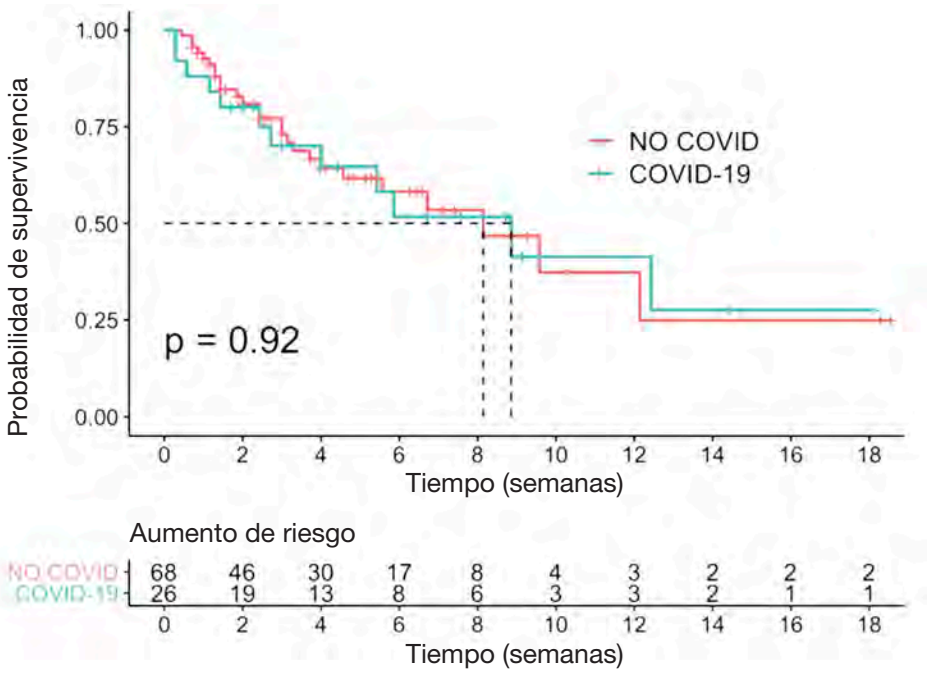

Figura 1 | **Supervivencia en paciente con bacteriemia por *S. aureus* por grupos.**

de los pacientes con BSA estaban co-infectados por COVID-19, lo que corresponde al 0,9% de los ingresados por COVID-19, siendo un porcentaje muy similar al obtenido por Cusumano JA *et al* (1,6%) [3]. Estos datos sugieren que esta infección podría ser en estos pacientes ligeramente más prevalente, un 2,8% más que en los pacientes no infectados (11,4% vs 8,8%) [11], ya sea por una predisposición relacionada con el propio virus a este tipo de infección o con el tipo especial de manejo que estos pacientes requieren.

S. aureus fue el segundo agente etiológico más frecuente de bacteriemia en nuestro estudio, sólo por detrás de *E. coli*. A diferencia de otros estudios que muestran un aumento de las bacteriemias por Gram negativos y disminución de las bacteriemias por grampositivos, especialmente *S. aureus* y *Staphylococcus* coagulasa negativos [12,13].

La tasa de contaminación de los hemocultivos se considera un indicador de la calidad asistencial y no debería sobrepasar el 3% de los hemocultivos totales recibidos [14]. En nuestro estudio se superó esta cifra, este hecho podría explicarse por la no familiaridad del personal sanitario con los equipos de protección individual (EPIs) así como por la alta rotación del personal que se produjo durante la pandemia.

La BSA en los pacientes con COVID-19 se produjo principalmente en mayores de 65 años y mayoritariamente en varones, hechos que se corresponden con el global de casos COVID-19 que ingresan en nuestro país, sin que esto marque alguna diferencia con el resto de BSA [11,15,16].

Las comorbilidades de los pacientes con COVID-19 de nuestra muestra difieren de las características clínicas de los pacientes con COVID-19 que ingresaron en nuestro país, donde la dislipemia y la diabetes mellitus fueron menores, 39,7% y 19,4% respectivamente [13], lo que sugeriría que estas comorbilidades pudieran predisponer a la BSA [3,9].

El hecho de que transcurriera un periodo de tiempo superior en los pacientes con COVID-19 desde el ingreso hasta que el hemocultivo fuese positivo estaría relacionado con un origen nosocomial de la bacteriemia (88,5%), como ya ha sido observado por otros autores [3,11], y que podría deberse al tipo de manejo de estos pacientes, con una mayor utilización de catéteres venosos periféricos o maniobras invasivas. En los pacientes con BSA sin co-infección por coronavirus, sin embargo, el origen es con más frecuencia comunitario y relacionado con otros focos.

El foco de la infección fue en la mayoría de los casos desconocido en ambos grupos de pacientes, siendo la infección de piel y partes blandas la principal fuente conocida. A diferencia de lo que ocurrió en los pacientes con COVID-19, en los que el foco respiratorio tuvo un papel importante, en los pacientes sin COVID-19 el foco respiratorio no fue el causante de ninguna bacteriemia ($p<0.001$). Esto podría explicarse debido a que un gran número de pacientes con COVID-19 precisaron VMI, a diferencia de los pacientes no- COVID-19. Sin embargo, se sabe que *S. aureus* actúa sinérgicamente en todas las temporadas de influenza, aumentando la mortalidad y la gravedad de la enfermedad, pudiendo ocurrir lo mismo con esta infección viral [18].

El 15,4% de las BSA en COVID-19 eran debidas a SARM, de forma similar a lo ocurrido en los pacientes no co-infectados, hasta un 20,1% según las series [9], pero que implica un cierto riesgo de fracaso en el tratamiento inicial si no se tiene en cuenta esta contingencia. Así, el tratamiento antibiótico empírico fue inadecuado en un elevado número de casos y los más utilizados como dirigidos, una vez conocido el antibiograma, fueron daptomicina y cefazolina, utilizando biterapia en un número elevado de casos, sin que esta estrategia haya demostrado un mejor pronóstico y sin que se realizara de forma preferente en uno u otro grupo. Sin embargo, la duración del tratamiento en no-COVID-19 fue 5 días superior, quizás explicado porque el tipo de foco de origen en los COVID-19 se controló con terapias más cortas (bacteriemia asociada a catéter en la mayoría de las ocasiones).

El 26,9% y 46,1% de los COVID-19 recibieron tratamiento con dexametasona con pauta d1 y d2 respectivamente, y el 23% con tocilizumab, lo que implica un número importante de casos sometidos a inmunosupresión durante el ingreso y lo que explicaría que estos pacientes tuvieran con más frecuencia un cuadro de sepsis, sobre todo aquellos en los que utilizó una pauta d2 (62,5% vs 37,5%) [19,20].

En cuanto a la evolución, el 34,6% de los pacientes con COVID-19 requirieron ingreso en UCI y VMI, datos muy similares a los registrados a nivel nacional (33,1% desarrolló distrés respiratorio) [15].

La mortalidad global (46%) y la mortalidad antes de los 14 días (30%) resultó mayor en los pacientes con COVID-19, sin ser estadísticamente significativo, siendo superior también a los registros globalmente de estos pacientes a nivel nacional (21%), por lo que parece claro que la contingencia de una BSA podría empeorar el pronóstico de estos pacientes. Parece que la mortalidad es superior en los que presentan un cuadro de sepsis (91,6% vs 8,3%), y va aumentando con la edad, como ocurre en los casos COVID-19 en nuestro medio (50-59 años: 4,7%; 60-69 años: 10,5%; 70-79 años: 26,9%; ≥ 80 años: 46%) [15], por lo que estos factores quizás puedan ayudar a seleccionar aquellos que pudieran tener una peor evolución.

La principal limitación que se aprecia en este estudio es la falta del cálculo del tamaño muestral para poder detectar diferencias entre los grupos. Esto se refleja en los resultados, donde en varias variables, existen diferencias entre grupos, pero sin alcanzarse la significación estadística, no pudiendo obtener conclusiones firmes. Otra de las limitaciones de este estudio es el elevado número de episodios de BSA de origen desconocido. La mayoría de estos episodios probablemente se tratasen de bacteriemias asociadas al catéter periférico (donde *S. aureus* es el agente causal más frecuente) sin poder documentarlo por no enviarse al laboratorio de microbiología cuando se extraen los catéteres periféricos, infradiagnosticando los casos de BRC. Este dato pone en alerta la necesidad de vigilancia más estrechad el manejo de estos accesos venosos en los pacientes con COVID-19.

Hasta un 0,9% de los ingresados por COVID-19 presentaron BSA. *S. aureus* fue el segundo agente causal en frecuencia de las bacteriemias en pacientes con COVID-19. La bacteriemia nosocomial fue más frecuente en los pacientes co-infectados por coronavirus del mismo modo que el foco respiratorio. El desarrollo de sepsis fue mayor en el grupo de pacientes con COVID-19, especialmente en aquellos que se utilizó una pauta con dosis altas de corticoides. En este estudio no se han encontrado diferencias estadísticamente significativas en cuanto a la mortalidad, sin embargo, se observa una tendencia hacia la mayor supervivencia de los pacientes no- COVID-19.

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CONFLICTOS DE INTERÉS

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Clindamycin but not Intravenous Immunoglobulins reduces mortality in a retrospective cohort of critically ill patients with bacteremic Group A Streptococcal infections

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ABSTRACT

Objectives. Mortality of patients requiring Intensive Care Unit (ICU) admission for an invasive group A streptococcal (GAS) infection continues being high. In critically ill patients with bacteremic GAS infection we aimed at determining risk factors for mortality.

Patients and methods. Retrospective multicentre study carried out in nine ICU in Southern Spain. All adult patients admitted to the participant ICUs from January 2014 to June 2019 with one positive blood culture for *S. pyogenes* were included in this study. Patient characteristics, infection-related variables, therapeutic interventions, failure of organs, and outcomes were registered. Risk factors independently associated with ICU and in-hospital mortalities were determined by multivariate regression analyses.

Results. Fifty-seven patients were included: median age was 63 (45-73) years, median SOFA score at admission was 11 (7-13). The most frequent source was skin and soft tissue infection (n=32) followed by unknown origin of bacteremia (n=12). In the multivariate analysis, age (OR 1.079; 95% CI 1.016-1.145), SOFA score (OR 2.129; 95% CI 1.339-3.383) were the risk factors for ICU mortality and the use of clindamycin was identified as a protective factor (OR 0.049; 95% CI 0.003-0.737). Age and SOFA were the independent factors associated with hospital mortality however the use of clindamycin showed a strong trend but without reaching statistical significance (OR 0.085; 95% CI 0.007-1.095).

Conclusion. In this cohort of critically ill patients the use of intravenous immunoglobulin was not identified as a protective factor for ICU or hospital mortality treatment with clindamycin significantly reduced mortality after controlling for confounders.

Keywords: Clindamycin; Intravenous Immunoglobulins; Bacteriemia; Critically ill patients; Group A Streptococcal infections.

Tratamiento con clindamicina, y no con inmunoglobulinas intravenosas, disminuye la mortalidad en una cohorte retrospectiva de pacientes críticos con bacteriemia por *Streptococcus* del Grupo A

RESUMEN

Objetivo. La mortalidad de los pacientes que requieren ingreso en la Unidad de Cuidados Intensivos (UCI) por una infección invasiva por estreptococos del grupo A (GAS) continúa siendo inaceptablemente alta. El objetivo del estudio fue determinar los factores de riesgo de mortalidad en pacientes críticos con infección estreptocócica bacterémica del grupo A.

Pacientes y métodos. Estudio retrospectivo multicéntrico realizado en nueve UCI del sur de España. Se incluyeron pacientes consecutivos ingresados en las UCI participantes desde enero de 2014 hasta junio de 2019 con un hemocultivo positivo para *S. pyogenes*. Se registraron las características de los pacientes, las variables relacionadas con la infección, las intervenciones terapéuticas, el fracaso de los órganos y el pronóstico. Se determinaron mediante análisis de regresión multivariante los factores de riesgo asociados de forma independiente con la mortalidad en UCI y hospitalaria.

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Resultados. Se incluyeron cincuenta y siete pacientes: la mediana de edad fue de 63 (45-73) años, la mediana de la puntuación SOFA al ingreso fue de 11 (7-13). El foco más frecuente fue la infección de la piel y los tejidos blandos (n=32) seguida de la bacteriemia de origen desconocido (n=12). En el análisis multivariante, la edad (OR 1,079; IC del 95%: 1,016-1,145), y la puntuación SOFA (OR 2,129; IC del 95%: 1,339-3,383) se identificaron como factores de riesgo para la mortalidad en UCI. El uso de clindamicina se identificó como un factor protector (OR 0,049; IC del 95%: 0,003-0,737). La edad y la SOFA se asociaron de forma independiente con la mortalidad hospitalaria, mientras que el tratamiento con clindamicina mostró una tendencia fuerte pero sin alcanzar significación estadística (OR 0,085; IC del 95%: 0,007-1,095).

Conclusión. En esta cohorte de pacientes críticos, el uso de inmunoglobulina intravenosa no se identificó como un factor protector para la mortalidad en UCI u hospitalaria, el tratamiento con clindamicina redujo significativamente la mortalidad después de controlar los factores de confusión

Palabras clave: Clindamicina; inmunoglobulinas intravenosas; Bacteriemia; pacientes críticos; infecciones estreptococos grupo A

INTRODUCTION

In spite of the advances in modern medicine, invasive group A streptococcal (GAS) infections cause a significant morbidity and mortality. Even though the resistance rates of GAS (*Streptococcus pyogenes*) to several antibiotics vary considerably worldwide, GAS remains universally susceptible to β-lactams antibiotics including penicillin [1], the lethality of severe invasive GAS infections requiring ICU admission remains high, about 50% in different series [2]. In these severe forms, *S. pyogenes* exotoxins act as superantigens to trigger polyclonal T-cell activation, cytokine cascade, shock, and death [3].

The low incidence of the invasive GAS disease explains the difficulties of randomized controlled trials evaluating management strategies. Likewise, observational cohort studies have been carried out using the majority of them administrative databases [4-6]. Moreover, conflicting results have been reported about the impact on mortality of different therapeutical strategies, specifically with the use of clindamycin or immunoglobulins [5,6].

In order to contribute to our knowledge about risk factors associated with mortality of severe invasive GAS infections, we performed this multicenter study including only patients admitted to the ICU. Our purposes were to stablish predictors of death carefully examining the clinical impact of antimicrobial strategies and the use of immunoglobulins on mortality after controlling for confounding variables.

METHODS

This is a retrospective multicenter study carried out in nine Spanish Intensive Care Units in Andalusia. The study was approved by the Spanish Agency of Medicinal Products and Medical Devices and by the local institutional review boards; written patient consent was not required because of the retrospective nature of this study.

All adult patients (≥18 years) admitted to the participant ICUs from January 2014 to June 2019 with one positive blood culture for *S. pyogenes* were included in this study. Patient baseline characteristics, infection-related variables and subsequent evolution were obtained from the automated hospital medical record and microbiology database of the participating centers. All patients were followed up for 90 days after the admission to the ICU for invasive GAS.

The following data were collected: age, gender, source of infection (skin and soft tissue, lung, unknow origin, and others) and underlying diseases: diabetes mellitus, liver cirrhosis, chronic renal disease, chronic heart failure, chronic obstructive pulmonary disease, and cancer. Severity of illness at ICU admission was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and by the Sequential Organ Failure Assessment (SOFA) scale considering the worst data point of the first 24 h in the ICU [7,8]. Clinical presentation was classified as sepsis or septic shock following Sepsis-3 definitions. The presence of a SOFA score of each organ >3 points at admission or during the ICU stay was considered as failure of this organ [9].

Data regarding management of these patients were also gathered: empirical antimicrobial regimen, use of clindamycin or linezolid, use of penicillin G as the β-lactam in directed therapy, administration of intravenous immunoglobulins (IVIG), mechanical ventilation and need of renal replacement therapy. In patients with skin and soft tissue infection (SSTI), date of the first surgical debridement and the total number of surgical interventions were also noted.

Standard microbiological methods were used by all the participating centers. This included the use of an automated continuous monitoring blood culture system, the performance of standard identification biochemical test, Lancenfield antigen immunoassay detection or, automated rapid test such as matrix-assisted laser desorption ionization-time of flight mass spectrometry (Maldi-tof). Susceptibility testing was performed using accepted methods at each hospital and results were interpreted according to the Clinical Laboratory Standard Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

Statistical analysis. Qualitative variables are presented as the absolute numbers and frequency, quantitative variables as mean (± SD) if their distribution was normally distributed or as median (percentile 25 – percentile 75) if the distributions were skewed. Student's t test was used to compare continuous variables with normal distribution, U Mann-Whitney tests for skewed distributed variables. Chi-2 and Fisher's exact tests were used for comparisons of categorical variables. Logistic regression models using variables with a p value <0.2 in the univariate analysis and those considered potentially relevant were used to determine the factors independently associated with ICU and in-hospital mortalities. All comparisons were two-tailed and signification was set at $p<0.05$.

SPSS 15.0 software (IBM SPSS, Chicago, IL, USA) was used for statistical analysis.

This analysis is reported following the STROBE recommendations [10].

RESULTS

During the study period, 57 patients were diagnosed of invasive GAS in the participant ICUs. The median age was 63 (45-73) years and 70.2 % were male. Median SOFA score at admission was 11 (7-13). The median time from hospital admission to positive blood culture was 0 (0, 1) days and the time elapsed from positive blood culture to ICU admission was 0 days (-1, 0). Twenty-eight patients (49.1%) died in the ICU, 30 patients (52.6%) during hospitalization, and mortality rate at 90 days was 64.9% (37 patients).

All patients had received empirical antibiotic treatment with a β-lactam antibiotic active against *S. pyogenes*. Bivariate analyses for ICU and hospital mortality are shown in Table 1. At baseline, there were no significant differences in sex, comorbid illnesses (except liver cirrhosis), or site of infection between survivors and non-survivors. All isolates were susceptible to penicillin although only 23 patients received penicillin G in the directed therapy. Eleven patients received IVIG and all of them were treated with clindamycin as well. All patients treated with clindamycin received this antibiotic during the first 48 hours after blood culture collection. In the multivariate analysis, two variables were identified as risk factors for ICU death meanwhile treatment of clindamycin was a protective factor (Table 2). Results of the multivariate analysis for hospital mortality is also depicted in the Table 2. Notably, use of IVIG was not identified as a protective factor for ICU or hospital mortality.

The comparison of clindamycin-treated patients and those who did not receive clindamycin is shown in table 3. Median duration of therapy with clindamycin was 7 days. Of note, clindamycin was more frequently used in patients with SSTI as source of bacteremia.

In the present study, the most frequent organ failure was cardiovascular, followed by respiratory (n=29) and renal failure (n=29). The incidence of other failure of organs was lower: coagulation (23.2%), central nervous system (22.8%), and hepatic failure (12.3%). The median number of organs failing in a patient was 2 (1-4). In our series, 41/57 (71.9%) required invasive mechanical ventilation and 28/57 (49.1%) needed continous renal replacement therapy (CRRT). Table 4 depicts the association between failure of the different organs and mortality.

DISCUSSION

Our multicenter study including severely ill patients with high-grade of organ dysfunction secondary to bacteremic invasive GAS confirms that this infection has a significant morbidity and a high mortality rate. Importantly, clindamycin as part of the antimicrobial therapy significantly reduced mortality after controlling for confounders while we could not demonstrate a beneficial effect of IVIG and survival was similar in patients who did or did not receive IVIG.

To the best of our knowledge, there is a paucity of studies carried out in patients with GAS requiring ICU admission. In our series, mortality rate is very high dying in the hospital 50% of the patients admitted to the ICU with this infection. These high figures have been reported previously by other authors. As an exception, an observational study reported an ICU mortality rate as low as 5.7% and even lower than the mortality of a heterogeneous group of septic patients. Importantly, only 60% of these 53 patients with invasive GAS presented septic shock and the rate of bloodstream infection is not reported by the authors [11].

Because the mortality rate with invasive GAS remains high, the therapeutical approach must be prompt and aggressive. In the present study, clinical and demographic characteristics were similar between patients treated and not treated with clindamycin, with the exception that severity of illness assessed by APACHE II score was significantly higher in the non-clindamycin group. Nevertheless, although severity of illness at admission to the ICU is a strong predictor of death in critically ill septic patients [12], treatment with clindamycin was a protective factor after controlling for confounding variables. Two observational studies have concluded that clindamycin improves survival in patients with invasive GAS [5,6]. A large observational study of patients with GAS infection has recently confirmed the reduction of mortality with the administration of clindamycin and this beneficial effect was present also present if the patient was not in septic shock or in another source of infection different to SSTI [13]. Conversely, a retrospective study evaluating patients with invasive GAS admitted to the ICU, the use of clindamycin was not associated with a better survival [14]. Linezolid is another theoretical alternative with a mechanism of action similar to that of clindamycin [15]. The experience with this oxazolidinone in invasive GAS is scarce but our findings do not support its use in invasive GAS for toxin synthesis inhibition.

The current surviving sepsis guidelines for adults recommends against the use of IVIg in patients with sepsis and septic shock [16]. However, the role of IVIG in patients with streptococcal septic shock has been a moot point during the last years. The largest observational study using propensity score matching and involving 4,127 patients with necrotizing fasciitis and streptococcal toxic shock concluded that IVIG had no effect on mortality or length of hospital stay [17]. The aforementioned studies about the beneficial effect of clindamycin also concluded that the use of IVIG was associated with higher survival [5,6]. A multicenter, randomized, double-blinded, placebo-controlled trial of IVIG in SSTI was prematurely stopped due to the lack of recruitment after enrolling only 21 patients [18].

SSTI and pneumonia were the most common sites of infection at presentation. In our series, source of infection does not have a prognostic value. Nevertheless, bacteremia without an identified focus was independently associated with an increased risk of a fatal outcome in a heterogenous group of

Table 1 **Bivariate Analysis for ICU Mortality and Hospital Mortality.**

	ICU mortality			In-hospital mortality		
Variables	Non-survivors (n=28)	Survivors (n=29)	p value	Non-survivors (n=30)	Survivors (n=27)	p value
Age (years)	68 (61-75)	52 (44-70)	0.006	69 (61-75)	52 (43-67)	0.002
Sex (man)	16 (57.1%)	24 (82.8%)	0.035	18 (60%)	22 (81.5%)	0.077
Underlying diseases						
Diabetes	10 (35.7%)	9 (31%)	0.708	11 (36.7%)	8 (29,6%)	0.574
Cirrhosis	4 (14.3%)	0 (0%)	0.035	4 (13.3%)	0 (0%)	0.049
Immunosuppression	4 (14.3)	5 (17.2%)	0.760	5 (16.7%)	4 (14,8%)	0.484
Chronic Heart Failure	3 (10.7%)	6 (20.7%)	0.302	4 (13.3%)	5 (18,5%)	0.592
Chronic Kidney Disease	5 (17.9%)	3 (10.3%)	0.414	5 (16.7%)	3 (11,1%)	0.547
Cancer	7 (25%)	5 (17.2%)	0.473	8 (26.7)	4 (14,8%)	0.273
COPD	6 (21.4%)	4 (13.8%)	0.449	5 (16.7%)	5 (18,5%)	0.854
Source of iGAS						
Skin and soft tissue	14 (50.0%)	18 (62.1%)	0.515	16 (53.3%)	16 (59.3%)	0.622
Unknown	8 (28.6%)	4 (13.8%)		8 (26.7%)	4 (14.8%)	
Lung	4 (14.3%)	5 (17.2%)		4 (13.3%)	5 (18.5%)	
Other	2 (7.2%)	0 (0%)		4 (13.3%)	2 (7.4%)	
APACHE II score at ICU admission	29 (22-32)	21 (16-25)	0.000	29 (22-32)	21 (16-25)	0.001
SOFA score at ICU admission	13 (11-15)	8 (6-10)	0.000	13 (11-15)	8 (6-10)	0.000
Respiratory	3 (2-3)	1 (1-2)	0.006	3 (2-3)	2 (1-2)	0.094
Cardiovascular	4 (3-4)	3 (1-4)	0.020	4 (3-4)	3 (1-4)	0.039
Renal	3 (2-4)	2 (1-2)	0.009	2 (2-4)	2 (1-3)	0.039
Coagulation	1 (0-2)	1 (0-2)	0.565	1 (0-2)	1 (0-2)	0.126
Liver	1 (0-2)	1 (0-2)	0.328	1 (0-2)	1 (0-2)	0.151
Central Nervous System	1 (1-3)	0 (0-0)	0.000	2 (1-2)	0 (0-0)	0.000
Worst SOFA score in the ICU	15 (12-17)	10 (6-11)	0.000	15 (12-16)	10 (6-12)	0.000
Respiratory	4 (3-4)	2 (1-2)	0.000	3 (2-4)	2 (1-3)	0.053
Cardiovascular	4 (4-4)	4 (3-4)	0.016	4 (4-4)	4 (3-4)	0.058
Renal	4 (2-4)	2 (1-4)	0.003	4 (2-4)	2 (1-4)	0.039
Coagulation	2 (0-3)	2 (0-2)	0.667	2 (0-3)	2 (0-2)	0.346
Liver	2 (0-2)	1 (0-2)	0.362	2 (0-2)	1 (0-2)	0.224
Central Nervous System	2 (1-4)	0 (0-1)	0.000	2 (1-4)	0 (0-1)	0.000
Therapeutic approach						
Clindamycin	14 (50%)	25 (86.2%)	0.003	16 (53.3%)	23 (85.2%)	0.010
Linezolid	7 (25%)	8 (27.6%)	1	8 (26.7%)	7 (25.9%)	1
Penicillin G in directed therapy	9 (32.1%)	14 (48.3%)	0.215	10 (33.3%)	13 (48.1%)	0.255
Immunoglobulin	6 (21.4%)	5 (17.2%)	0.689	6 (20%)	5 (18.5%)	0.887
Mechanical ventilation	28 (100%)	13 (44.8%)	0.000	28 (93.3%)	13 (48.1%)	0.000
Renal Replacement Therapy	18 (64.3%)	10 (34.5%)	0.024	17 (56.7%)	11 (40.7%)	0.230

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; iGAS: invasive group A *Streptococcus*.

Table 2 Factor independently associated with ICU and Hospital Mortality in the multivariate analysis

ICU MORTALITY	OR	CI 95%	p
Age	1.079	1.016-1.145	0.013
Use of clindamycin	0.049	0.003-0.737	0.029
SOFA	2.129	1.339-3.383	0.001
HOSPITAL MORTALITY			
Age	1.092	1.026-1.162	0.005
Use of clindamycin	0. 085	0.007-1.095	0.085
SOFA	2.089	1.345-3.246	0. 001

non-critically ill patients with a mortality rate much lower than ours (14%) [19].

Our data also highlight that the high incidence and the severity of organ failures in patients with invasive GAS requiring ICU admission explaining the high mortality and the burden of care associated with this disease. In our series, degree of organ disfunction assessed by SOFA score is an independent predictor of ICU and hospital mortality. Similarly, the number of dysfunctional organs correlated with mortality being coagulopathy and liver failure factors independently associated with mortality [14]. Invasive mechanical ventilation was used in two-thirds of our patients and 50% of them fulfilled criteria of severe respiratory failure. Likewise, half of the patients developed acute renal failure requiring CRRT. Information regarding failure of organs is lacking in previous studies that have observed the beneficial effect of clindamycin in invasive GAS [5,6,13]. The SOFA score as a mortality estimation tool presents a high discriminatory capacity to predict ICU mortality [20].

We acknowledge several limitations of this study. First, this is a retrospective study and as our sample size was relatively small for some comparisons, a type II error is possible. Second, the gold standard for demonstrating that a therapeutic intervention impacts on the outcome is a randomized, controlled, blinded trial. Nevertheless, observational studies can provide valuable information about treatment effectiveness especially in infections with low frequency of presentation. Third, although we could not demonstrate a beneficial impact of immunoglobulins on survival both the quantity and quality of neutralizing antitoxin antibodies vary from batch to batch of IVIG what may have influence our negative findings [21]. Fourth, sequencing of the variable M serotype–specific region of the *emm* gene has not been carried out in our study. This is important since certain GAS *emm* sequence types have been associated with mortality [22,23].

To sum up, our findings are of the utmost importance since, in this cohort of critically ill patients with multiple organ dysfunction secondary to bacteremic GAS, we have demonstrated the beneficial effect in terms of mortality of adding clindamycin as part of the antimicrobial management. In these

Table 3 Comparison of clindamycin-treated patients and those who did not receive this antibiotic

Variables	Clindamycin (n=39)	No clindamycin (n=18)	p value
Age (years)	61 (44-73)	68 (61-75)	0.091
Sex (man)	28 (71.8%)	12 (66.7%)	0.694
Underlying diseases			
Diabetes	12 (30.8%)	7 (38.9%)	0.546
Cirrhosis	0	4 (22.2%)	0.002
Immunosuppression	6 (15.4%)	3 (16.7%)	0.902
Chronic Heart Failure	5 (12.8%)	4 (22.2%)	0.366
Chronic Kidney Disease	6 (15.4%)	2 (11.1%)	0.666
Cancer	8 (20.5%)	4 (22.2%)	0.883
COPD	4 (10.3%)	6 (33.3%)	0.033
Source of iGAS			
Skin and soft tissue	26 (66,7%)	6 (33.3%)	0.031
Unknown	7 (17.9%)	5 (27,8%)	
Lung	5 (12,8%)	4 (22.2%)	
Others	1 (2.6%)	3 (16,7%)	
APACHE II score at ICU admission	29 (22-32)	21 (16-25)	0.000
SOFA score at ICU admission	13 (11-15)	8 (6-10)	0.000
Respiratory	3 (2-3)	1 (1-2)	0.006
Cardiovascular	4 (3-4)	3 (1-4)	0.020
Renal	3 (2-4)	2 (1-2)	0.009
Coagulation	1 (0-2)	1 (0-2)	0.565
Liver	1 (0-2)	1 (0-2)	0.328
Central Nervous System	1 (1-3)	0 (0-0)	0.000
Worst SOFA score in the ICU	10 (7-12)	13 (7-15)	0.130
Respiratory	2 (1-3)	2 (1-3)	0.180
Cardiovascular	4 (3-4)	3 (1-4)	0.360
Renal	2 (1-3)	2 (2-3)	0.785
Coagulation	1 (0-2)	1 (0-2)	0.413
Liver	1 (0-2)	1 (0-2)	0.221
Central Nervous System	0 (0-1)	1 (0-3)	0.026
Therapeutic approach			
Linezolid	15 (38.5%)	8 (44.4%)	0.669
Penicillin G in directed therapy	21 (53.8%)	2 (11.1%)	0.002
Immunoglobulin	11 (28.2%)	0	0.012
Mechanical ventilation	26 (66.7%)	15 (83.3%)	0.193
Renal Replacement Therapy	19 (48.7%)	9 (50%)	0.928
ICU mortality	14 (35.9%)	14 (77.8%)	0.003
Hospital mortality	16 (41%)	14 (77.8%)	0.010
90-day mortality	23 (60.5%)	14 (77.8%)	0.203

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; iGAS: invasive group A *Streptococcus*.

Table 4 **Association between failure of the different organs and ICU and Hospital mortalities.**

	ICU mortality			In-hospital mortality		
Organ Failure	Non-survivors (n=28)	Survivors (n=29)	p value	Non-survivors (n=30)	Survivors (n=27)	p value
Respiratory failure	22 (78.6%)	7 (24.1%)	<0.001	21 (70%)	8 (29.6%)	0.002
Renal failure	19 (67.9%)	10 (34,5%)	0.012	18 (60%)	11 (40,7%)	0.146
Cardiovascular failure	27 (96.4%)	22 (75.9%)	0.025	28 (93.3%)	21 (77.8%)	0.091
Liver failure	5 (17.9%)	2 (6.9%)	0.208	6 (20%)	(3.7%)	0.061
Coagulation failure	9 (32.1%)	4 (13.8%)	0.099	10 (33.3%)	3 (11.1%)	0.046
Central Nervous System failure	12 (42.9%)	1 (3.4%)	<0.001	13 (43.3%)	0	<0.001

ICU: Intensive care unit

patients, we were unable to determine that IVIG has a beneficial effect. Due to the significant morbidity and mortality of invasive GAS infections, further studies are warranted to define the role new therapeutic strategies to improve the somber prognosis of bacteremic invasive GAS.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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La infección congénita por citomegalovirus, ¿es más prevalente en nuestro medio en neonatos expuestos al VIH?

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RESUMEN

Objetivos. La infección congénita por citomegalovirus (CMVc) se ha considerado más prevalente en hijos de madre infectadas por VIH (RNEVIH). Por ello, las guías nacionales aconsejan el cribado del CMVc en el RNEVIH. Actualmente estas gestantes en España presentan mejor control de la infección que en décadas precedentes, pudiendo afectar a dicha prevalencia. El objetivo del estudio es analizar la prevalencia y posibles factores de riesgo asociados a la CMVc en RNEVIH en la era del tratamiento antirretroviral combinado (TAR).

Pacientes y métodos. Estudio transversal retrospectivo, incluyendo todos los hijos de madre con VIH nacidos en un hospital de tercer nivel (2014-2020). Se recogieron datos epidemiológicos y clínicos de la madre y del neonato. Se realizó cribado neonatal de CMV con cultivo de orina *shell vial* y/o PCR en las 2 primeras semanas de vida.

Resultados. Se incluyeron 69 neonatos. El 82,4% de las madres habían sido diagnosticadas de VIH previamente al embarazo. Todas recibieron TAR durante la gestación. La mediana de linfocitos T-CD4 previos al parto fue 641/mm^3 (RIC: 480-865) y la CV fue indetectable en el 83,6%. La serología para CMV en el primer trimestre se realizó en el 73,5% (IgG positiva en el 96%). No hubo casos de transmisión vertical de VIH ni CMVc (IC 95%: 0-5,3%).

Conclusiones. La prevalencia de CMVc en neonatos expuestos al VIH en nuestra cohorte fue del 0%, inferior a la documentada en estudios previos, posiblemente en relación con el acceso precoz al TAR en las gestantes y su buena situación inmunológica.

Palabras clave: infección congénita por citomegalovirus, hijo de madre infectada por VIH.

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Congenital cytomegalovirus infection, is more prevalent in our country in newborns exposed to HIV?

ABSTRACT

Objectives. Congenital cytomegalovirus infection (cCMV) has been considered more prevalent among HIV-exposed children during pregnancy. Spanish national guidelines recommend the cCMV screening in these newborns. Nowadays, pregnant women have a better control of HIV infection compared to previous decades. We aim to analyze the prevalence and associated risk factors to cCMV in these children.

Patients and methods. A retrospective cross-sectorial study was performed. All newborns exposed to HIV were assisted in a third-level hospital (2014-2020). Epidemiological and clinical data of the mother and newborn were recorded. Shell vial urine culture and/or CRP were performed along the two first weeks of life for the neonatal screening of cCMV.

Results. Overall 69 newborns were enrolled. A high proportion (82.4%) of the mothers had been diagnosed with HIV before getting pregnant. All women received ART during the pregnancy. Median T-CD4 lymphocytes before delivery was 641/mm^3 (IQR: 480-865) and the viral load was undetectable in 83.6%. Serological test for CMV along the first trimester of pregnancy was performed in 73.5% (positive IgG in 96%). There were no congenital cases of HIV neither cCMV (CI 95%: 0-5.3%).

Conclusions. The cCMV prevalence in newborns exposed to HIV was 0%, lower than reported before, probably related to a better and earlier ART during pregnancy, leading to a better immunological status.

Keyword: congenital cytomegalovirus infection, newborn HIV exposed.

INTRODUCCIÓN

El citomegalovirus (CMV) es la principal causa de infección congénita en la actualidad en todo el mundo, afectando aproximadamente al 0.2-2.2% de los recién nacidos vivos [1,2]. Se trata de la primera causa de hipoacusia de origen no genético en la edad pediátrica, produciendo asimismo secuelas desde el punto de vista del neurodesarrollo [2]. Los escasos estudios que han analizado la prevalencia de la infección congénita por citomegalovirus (CMVc) en neonatos hijos de madre con infección por el virus de la inmunodeficiencia humana (RNEVIH) sostienen que dicha prevalencia es mayor que en la población general con tasas que oscilan entre el 2,3 y el 6,5% en cohortes recientes, sin embargo algunas series han documentado hasta un 21-23,2% de prevalencia cuando se asocia la transmisión del VIH al recién nacido [3,4], con diferencias según el desarrollo del país y el nivel socioeconómico [5,6]. Asimismo, es posible que estos pacientes muestren síntomas con más frecuencia y una progresión más rápida de la infección por VIH [3,7–9].

En el estudio más relevante realizado en nuestro medio (1987-2003) [10] se documentó una prevalencia de CMVc del 4,6% en estos neonatos. Sin embargo, en este mismo estudio, conforme las gestantes accedieron al tratamiento antirretroviral combinado (TAR) y mejoraron el control de la infección por el virus de la inmunodeficiencia humana (VIH) la prevalencia de CMVc mostró un descenso significativo (1,3% en los últimos años del estudio) aproximándose a la prevalencia del CMVc en la población general.

Actualmente el documento de consenso nacional de varias sociedades científicas para el manejo del recién nacido expuesto al VIH aconseja la realización de cribado de CMVc en hijos de madre con VIH en las dos primeras semanas de vida [11]. Sin embargo, en los últimos años, no todas las recomendaciones de las sociedades científicas relevantes son coincidentes [12].

El objetivo principal del estudio es determinar la prevalencia en nuestro medio de CMVc entre los recién nacidos hijos de madre con infección por VIH en la era del TAR.

PACIENTES Y MÉTODOS

Diseño del estudio y participantes. Se realizó un estudio transversal retrospectivo en un hospital de tercer nivel en Madrid. Se incluyeron todos los recién nacidos expuestos a VIH intraútero y nacidos en nuestro centro entre enero de 2014 y diciembre de 2020. Se excluyó un paciente nacido en otro centro sanitario. Se recogieron todos los datos epidemiológicos y clínicos de las madres infectadas por VIH y sus respectivos neonatos; todos los datos fueron manejados en una base de datos anonimizada. El proyecto fue revisado y aprobado por el Comité de Ética y de Investigación del hospital. Dado que se trató de un estudio retrospectivo con datos anonimizados obtenidos a partir de un protocolo asistencial del centro, no se consideró necesaria la elaboración de un consentimiento informado.

Todas las madres y los neonatos fueron atendidos con un protocolo unificado según las guías nacionales de consenso, incluyendo TAR durante la gestación, profilaxis intraparto, exclusión de la lactancia materna, profilaxis del recién nacido, cribado auditivo del neonato y realización de cribado universal de CMVc [11,12].

Definiciones. Se definió como madre con infección por el VIH a todas aquellas gestantes con al menos una prueba microbiológica de cribado y una confirmatoria positivas, en muestras diferentes [13], previas o durante la gestación. Se las clasificó según el estadio de los CDC [14]. Se definió como buen cumplimiento terapéutico cuando la madre refería tomar adecuadamente el tratamiento antirretroviral añadido a un adecuado control de la CV y linfocitos CD4.

Se consideró CMVc a los neonatos con demostración microbiológica de la presencia del virus en muestra urinaria.

Los neonatos nacidos con más de 37 semanas de edad gestacional se consideraron a término. Los nacidos entre las 24-28 semanas se definieron como "pretérminos extremos", entre las 28-32 semanas "muy prematuros" y entre las 32-37 semanas "moderados o tardíos" [15]. Para valorar la antropometría de los recién nacidos, el peso, talla y perímetro cefálico fueron comparados con los estándares de los Estudios Españoles del Crecimiento (2010), para edad gestacional y sexo, definiendo bajo peso, talla o perímetro cefálico para edad gestacional cuando el percentil del paciente era <10, normal si 10-90 y elevado si >90 [16].

Con respecto a los valores analíticos, se consideró anemia cuando la hemoglobina (Hb) era menor a 15 g/dl en la analítica realizada en la primera semana de vida [17], hipertransaminasemia cuando los valores de aspartato-aminotransferasa (AST) >50U/L y/o alanina-aminotransferasa (ALT) >45U/L [18]. Niveles >150 U/L de gamma-glutamiltransferasa fueron considerados elevados [19].

Se definió hipoacusia cuando no se obtuvo onda V en los potenciales evocados de tronco encefálico a 40dB [20].

Se establecieron como posibles síntomas de CMVc la hipertransaminasemia, ictericia, petequias, hepatoesplenomegalia, microcefalia, hipoacusia, alteraciones en pruebas de imagen cerebral compatibles perinatales, siempre y cuando se demostrase la presencia de CMV en orina [1].

Diagnóstico. Para el diagnóstico de CMVc, se recogió muestra de orina mediante bolsa colectora en las dos primeras semanas de vida. Esta muestra fue estudiada por el servicio de Microbiología, realizando cultivo mediante *shell vial* (Vircell®, Granada, España) para CMV en muestras recogidas hasta febrero de 2018. A partir de septiembre de 2017 se realizó PCR para CMV en orina en todos los recién nacidos a través de Microlab STARlet® de Hamilton (Nevada, EUA).

Para valorar la transmisión vertical de VIH, se realizó PCR cuantitativa de ARN viral con el sistema Cobas 6800® de Roche Molecular Diagnostics (Pleasanton, EUA), estableciendo el límite de indetectabilidad cuando se documentaron

<20 copias/mL. Las PCR se realizaron al nacimiento, a la tercera o cuarta semana de vida, a las 4-6 semanas y entre los 3-4 meses. Se descartó la transmisión vertical cuando se obtuvieron al menos 2 pruebas PCR negativas a partir de las 6-8 semanas de vida, siendo alguna entre los 3-4 meses [11]. Asimismo se realizaron controles serológicos en el lactante durante el segundo año de vida para confirmar la ausencia de anticuerpos maternos a través de quimioluminiscencia con Atellica IM Analyzer® de Siemens Healthcare Diagnostics (Erlangen, Germany).

Análisis estadístico. Los resultados de frecuencia son expresados en términos absolutos, como porcentajes e intervalos de confianza. Las variables continuas serán expresadas como media y desviación estándar (DS) o bien mediana (rango intercuartílico), según distribución. Los datos fueron analizados usando el software de análisis estadístico SPSS 23.0.

RESULTADOS

A lo largo del periodo de estudio, se documentaron 39457 nacimientos en nuestro centro, con un total de 69 neonatos (0,17%) hijos de 68 madres seropositivas para VIH. La mayoría de las gestantes nacieron en España (38,2%), seguidas por las de origen latinoamericano (30,9%). Asimismo, la gran mayoría de las madres había sido diagnosticada de VIH antes de la gestación (82,4%); sólo dos de ellas a partir de la semana 20 de gestación (semana 20 y 22 respectivamente). Todas ellas recibieron TAR desde el inicio del embarazo, la mayoría con buen cumplimiento (91,2%). Más de la mitad de las gestantes presentaban estadios A1 y A2 de la clasificación de los CDC (26,5 y 27,9% respectivamente). Los datos epidemiológicos y clínicos de las madres se muestran en la Tabla 1 y 2 respectivamente. La pauta de tratamiento antirretroviral más frecuente a lo largo de la gestación fue 2 inhibidores de la transcriptasa inversa análogos de nucleósidos (ITIAN) + inhibidor de la integrasa (II) (35,3%), seguida por 2 ITIAN + inhibidores de la transcriptasa inversa no análogos de nucleósidos (ITINAN) (29,4%). Ocho mujeres (11,8%) recibieron raltegravir en las últimas semanas de la gestación para disminuir la carga viral dado que ésta era detectable en el último trimestre. Los esquemas de tratamiento antirretroviral maternos durante la gestación se muestran en la Figura 1.

En cuanto a los datos perinatales, más del 75% habían tenido uno o ningún hijo previamente. En un caso se detectó ventriculomegalia en la ecografía del segundo trimestre, sin encontrar otros hallazgos ecográficos. El 98,5% de las gestaciones fueron únicas, sólo hubo una gestación gemelar. El 80% de las madres presentó una carga viral indetectable en el tercer trimestre de la gestación, mientras que aquellas en las que fue detectable presentaban baja replicación, con una mediana de 445 copias/mm^3 (RIC: 37-865). Asimismo, la mediana de linfocitos T CD4 fue de 641/mm^3 (RIC 480-865). Hasta el 65% de los neonatos nacieron por cesárea; en todos los casos se administró profilaxis antirretroviral intraparto. Los datos perinatales se reflejan en la Tabla 3.

Tabla 1 **Datos epidemiológicos de las madres con infección por VIH.**

Total pacientes N = 68 (%)	N (%)
Edad (años)	35 (28-38)*
Origen	
Europea	29 (42,6%)
Latinoamericana	21 (30,9%)
Africana	18 (26,5%)
País de nacimiento	
España	26 (38,2%)
República Dominicana	7 (10,3%)
Guinea Ecuatorial	7 (10,3%)
Nigeria	5 (7,4%)
Ecuador	4 (5,9%)
Rumanía	3 (4,4%)
Cuba	2 (2,9%)
Perú	2 (2,9%)
Venezuela	2 (2,9%)
Colombia	1 (1,5%)
Costa de Marfil	1 (1,5%)
Guatemala	1 (1,5%)
Honduras	1 (1,5%)
Kenia	1 (1,5%)
Marruecos	1 (1,5%)
Paraguay	1 (1,5%)
Portugal	1 (1,5%)
Senegal	1 (1,5%)
Sierra Leona	1 (1,5%)

*Mediana (p25-75); IC 95%: intervalo de confianza al 95%.

No se documentó ninguna primoinfección por CMV durante la gestación. La serología para CMV se había realizado en 35/68 (51,5%) de las mujeres previamente a la gestación actual, resultando en 34/35 (97,1%) con IgG positiva. Durante la gestación, se realizó serología en el primer trimestre en 50/68 (73,5%) siendo en 47/50 (96%) IgG positiva con IgM negativa y en un caso IgM positiva con IgG positiva de alta avidez; las otras dos pacientes restantes fueron seronegativas para CMV.

Atendiendo a los neonatos, el 55,1% fueron mujeres. La mayoría fueron nacidos a término (85,5%). El peso mediano al nacimiento fue de 2980g (RIC: 2750-3300); la talla mediana fue de 48 cm (RIC: 46.5-49); respecto al perímetro cefálico, la mediana fue de 34 cm (RIC: 33-35). Los datos analíticos y clínicos de los neonatos se reflejan en la Tabla 4.

Ningún neonato presentó al nacimiento síntomas o

Tabla 2 **Datos clínicos de las madres infectadas por VIH.**

Total pacientes N = 68 (%)	N (%)
Tipo de transmisión del VIH	
Sexual	32 (47,1%)
Vertical	9 (13,2%)
UDVP	2 (2,9%)
Desconocido	25 (36,8%)
Estadio CDC	
A1	18 (26,5%)
A2	19 (27,9%)
A3	2 (2,9%)
B1	5 (7,4%)
B2	5 (7,4%)
B3	2 (2,9%)
C2	1 (1,5%)
C3	8 (11,8%)
Desconocido	8 (11,8%)
Cumplimiento TAR durante la gestación	
Adecuado	62 (91,2%)
Mala cumplidora	6 (8,8%)
Otros antecedentes	24 (35,3%)
Condilomas / verrugas genitales	8 (11,8%)
Candidiasis recurrente	6 (8,8%)
Herpes zóster recurrente	4 (5,9%)
Toxoplasmosis	3 (4,4%)
Condilomas / verrugas anales	3 (4,4%)
Tuberculosis	3 (4,4%)
Herpes genital	2 (2,9%)
Hepatitis B	2 (2,9%)
Esofagitis herpética	2 (2,9%)
Colitis por citomegalovirus	2 (2,9%)
Neumonía bacteriana	1 (1,5%)
Hepatitis C	1 (1,5%)
Neumonía por *Pneumocystis jiroveci*	1 (1,5%)
Citomegalovirus ocular	1 (1,5%)
Meningitis linfocitaria	1 (1,5%)
Absceso corneal por *P. aeruginosa*	1 (1,5%)
Usuaria de drogas no parenteral	7 (10,3%)
Mutaciones y resistencias a ARV	
Mutaciones sin resistencias:	
Transcriptasa inversa	10 (14,7%)
Proteasa	7 (10,3%)
Resistencias:	
EFV, NVP, 3TC/FTC	5 (7,4%)
NFV + intermedias: NVP, IDV/RTV, SQV/RTV, EFV	4 (5,9%)
3TC/FTC, SQV/RTV, IDV, NFV, APV	3 (4,4%)

IC 95%: intervalo de confianza al 95%; 3TC/FTC: Lamivudina/ Emtricitabina; APV: Amprenavir; ARV: antirretrovirales; EFV: Efavirenz; IDV/RTV: Indinavir/ Ritonavir; NFV: Nelfinavir; NVP: Nevirapina; *P. aeruginosa*: *Pseudomonas aeruginosa*; SQV/RTV: Saquinavir/ Ritonavir; TAR: terapia antirretroviral combinada; UDVP: usuaria de drogas vía parenteral

signos compatibles con CMVc. Asimismo, la mayor parte de los neonatos superaron las otoemisiones acústicas (97,1%), detectándose únicamente una hipoacusia grave de etiología no infecciosa.

En cuanto al estudio diagnóstico de CMV en orina, se recogió la muestra en todos los neonatos, siendo negativo en el 100% de los casos. La orina fue recogida con una mediana de 2 días de vida (RIC 1-3). Por otro lado, no se diagnosticó ningún caso de transmisión vertical de VIH siendo seguidos hasta presentar 3 PCR negativas y ELISA negativo (entre los 12 y 24 meses).

Todos los neonatos recibieron tratamiento profiláctico para la transmisión vertical de VIH al nacimiento. Los diferentes esquemas de profilaxis en el neonato se muestran en la Figura 2. La pauta más común fue zidovudina en monoterapia (81,2%) durante 28 días. La exclusión de la lactancia materna fue universal. Todos los neonatos fueron controlados en la consulta de Enfermedades Infecciosas de Pediatría del Hospital La Paz durante el seguimiento.

Según los hallazgos obtenidos, se estimó una prevalencia de CMVc en nuestra cohorte del 0%, con un intervalo de confianza al 95% de 0-5,3%.

DISCUSIÓN

Los resultados obtenidos en este trabajo demuestran una prevalencia de CMVc en neonatos con exposición al VIH del 0% en nuestra cohorte, inferior a la descrita previamente, incluso en situaciones sociodemográficas comparables.

Los principales estudios recientes han establecido prevalencias de CMVc entre neonatos expuestos a la infección por el VIH del 2,3 al 6,5%, sin embargo, se trata de cohortes de seguimiento realizadas a lo largo de muchos años [3,8,10,21]. Los pacientes con infección por el VIH de transmisión vertical confirmada presentan prevalencias superiores (10-26%) a los pacientes expuestos sin infección [3,8,10]. La situación de la salud global en las gestantes con infección por VIH ha variado de forma muy significativa respecto a los primeros años de la epidemia en España, en paralelo a la mejoría de las tasas de morbimortalidad de los pacientes con infección por VIH y de la reducción en las tasas de transmisión vertical materno-infantil.

Un estudio realizado en Madrid en 2005 obtuvo una prevalencia de CMVc del 4,6% en estos neonatos a lo largo de más de 15 años y del 1,3% en la época del TAR en particular [10]. Un trabajo posterior, llevado a cabo en la cohorte francesa [8] documenta una prevalencia del 1,5% en la era del TAR, con conclusiones similares al estudio previo. Éste cuenta con un tamaño muestral aún mayor que el estudio español, no obstante, las gestantes comienzan el tratamiento antirretroviral (ARV) en el segundo trimestre, con CD4 <200/ mm^3. Esta reducción de la prevalencia de CMVc con el uso de TAR no se ha confirmado, sin embargo, en otros estudios. T. Frederick *et al.* publican en el 2012 su investigación llevada a cabo en Los Ángeles (EEUU) y hallan una prevalencia del 3,6% sin encontrar diferencias significativas entre la época pre-TAR y la era TAR; en este trabajo también se incluye un

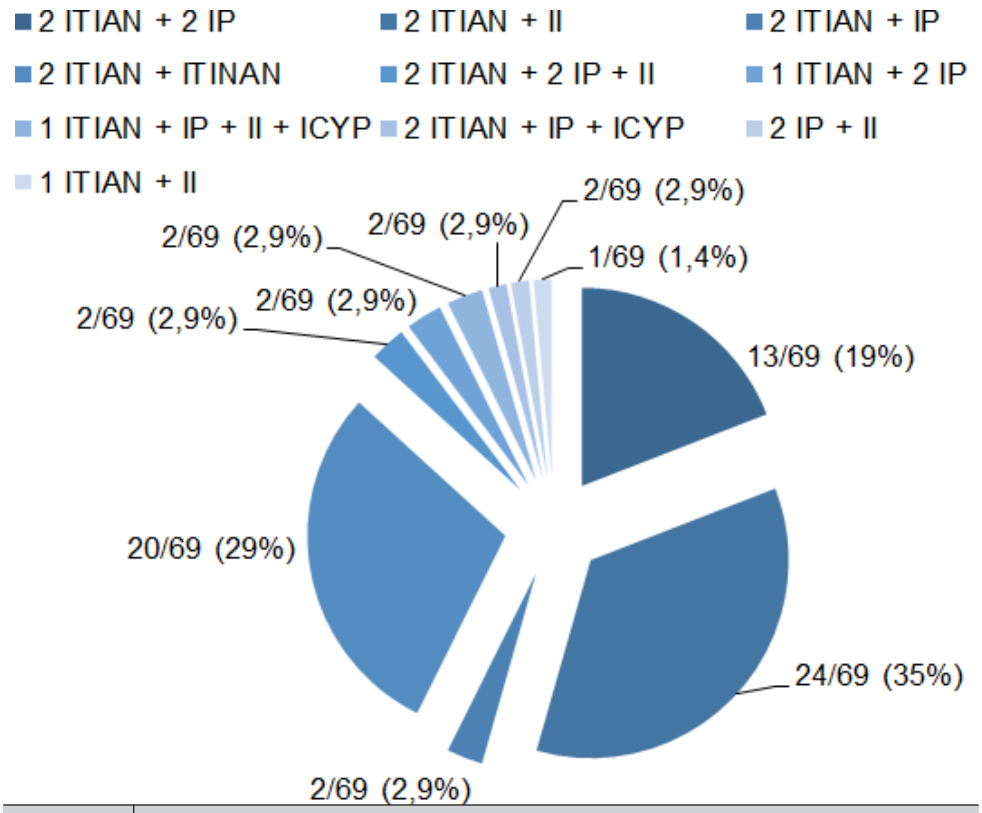

Figura 1 | **Tratamiento materno durante la gestación.**

ICYP: inhibidor del citocromo p450 3A; II: inhibidor de la integrasa; IP: inhibidor de la proteasa; ITIAN: Inhibidor de la transcriptasa inversa análogo de nucleósido; ITINAN: Inhibidor de la transcriptasa inversa no análogo de nucleósido.

alto porcentaje de gestantes que comienzan ARV en tercer trimestre lo que podría matizar las conclusiones [21]. Por otro lado, un trabajo llevado a cabo por un grupo brasileño [3], demostró incluso una prevalencia de CMVc del 6,5%, mayor que en los estudios previos. Este estudio incluye gestantes con alta carga viral de VIH y que no recibían ARV.

La disponibilidad del TAR desde el primer trimestre del embarazo se ha sugerido como un factor protector clave frente al CMVc en estos neonatos [8] así como su ausencia o la transmisión vertical del VIH al neonato suponen importantes factores de riesgo [3]. No obstante, un estudio reciente realizado en Sudáfrica no encontró relación con la duración del TAR materno ni con el estado de inmunosupresión materno. Aunque sí encontraron relación en la cotransmisión de ambos virus y mayor prevalencia de CMVc en neonatos expuestos intraútero a VIH. Como establecen estos autores, la ausencia de diferencia puede ser explicada por el reducido tamaño de pacientes con CMVc (N: 46) [22].

En nuestro estudio, el 92% de las gestantes conocían el diagnóstico de VIH previo a la gestación, por lo que pudieron recibir ARV desde el primer trimestre. Asimismo, nuestra cohorte presenta un adecuado cumplimiento terapéutico con unos CD4 superiores a los estudios comentados. Sólo 11 mujeres presentaron carga viral detectable en el último trimestre (la mayor de 2310 copias/ml), por lo que recibieron raltegravir para reducir ésta y sólo una paciente presentaba unos linfocitos CD4 <200/mm^3 en el último control (177 CD4//mm^3).

Del análisis de estos estudios y en consonancia con los resultados de nuestra cohorte, se concluye que la prevalencia del CMVc en este colectivo parece tener relación con el grado de inmunosupresión materno [6–8,23], ya sea por no recibir tratamiento o por presentar unos CD4 <200mm^3 e impresiona que en la era TAR, la prevalencia de CMVc se ha reducido siempre y cuando la madre cumpla adecuadamente con el tratamiento desde el inicio de la gestación [9].

Sin embargo, incluso en las cohortes con resultados más favorables de prevalencia de CMVc (1,3-1,5%), ésta parece superior a la prevalencia de CMVc en la población general en países desarrollados (0,4-0,7%) [24,25]. También en la literatura podemos encontrar estudios que hallan una prevalencia de CMVc en hijos de madre con VIH similar a los de la población general en países en vías de desarrollo (2,7 vs 2,9%), lo cual relacionan con la baja tasa de estadio SIDA de las madres infectadas por el VIH (8,7%) [26]. Recientemente Purswani *et*

Tabla 3 **Datos clínicos perinatales en los neonatos expuestos al VIH.**

Total madres	N= 68 (%)
Paridad previa	
0	27 (39,7%)
1	25 (36,8%)
2	9 (13,2%)
3	5 (7,3%)
Desconocido	2 (2,9%)
Gestación	
Única	67 (98,5%)
Gemelar	1 (1,5%)
Tipo de parto	
Cesárea	44 (64,7%)
Por infección por VIH	16 (36,4%)
Causa obstétrica	28 (63,6%)
Vaginal	24 (35,3%)
Instrumental	7 (10,3%)
Linfocitos T CD4 preparto	641/mm3 (480-865)*
Disponibles en	61 (89,7%)
Carga viral VIH preparto	
Disponible en	67 (98,5%)
Indetectable	56 (83,6%)
Detectables:	11 (16,2%)
copias/mL	445 (37-865)*
Profilaxis intraparto	
Zidovudina	66 (97,1%)
Zidovudina + nevirapina	2 (2,9%)

Todos los datos se muestran como valores absolutos (porcentaje relativo) salvo *Mediana (p25-75)

al. encuentran una prevalencia de CMVc de 0.9% en pacientes bien controladas [5], con tratamiento antirretroviral y la inmensa mayoría con linfocitos CD4 >200/mm^3.

Algunos estudios han tratado de dilucidar la posible asociación de fármacos antirretrovirales con la no transmisión de CMV al feto [5,23]. El grupo francés no encontró diferencias en los diferentes regímenes utilizados [8]. En nuestra cohorte, al no documentar pacientes con CMVc, no pudimos valorar si hubo diferencias entre los regímenes empleados.

Es bien conocido que la seroprevalencia de CMV en la población varía en función de la edad, geografía y raza, siendo mayor en áreas más desfavorecidas [3]. Un metaanalisis publicado en 2007 reportó que el CMVc podría ser más frecuente en los casos de primoinfección materna en lugar de reactivación [25]. Posteriormente, se han publicado artículos que documentan que el CMVc parece ser más frecuente por reactivaciones en la madre durante el embarazo [27]. El embarazo constituye un estadio de inmunosupresión materna, en el cual podría ocurrir dicha reactivación [28], si a esto se le añade la infección por VIH con mal control, ésto podría explicar que la CMVc en hijos de madre con VIH fuese más frecuente. En nuestro estudio, se realizó serología al 73,5% de las gestantes en el primer trimestre, encontrando una seroprevalencia IgG para CMV del 96%. Sin embargo, no encontramos ningún caso de CMVc, lo cual podría ser explicado por un adecuado control materno (mediana de linfocitos CD4 previos al parto: 641/mm^3 y 83.6% con carga viral indetectable). Algunos estudios establecen que las madres más jóvenes VIH-seropositivas son un factor de riesgo para el CMVc [8], por la mayor probabilidad de tener hijos de corta edad, con mayor riesgo de contagio.

Se ha postulado en varios estudios, que pueda existir una sinergia entre el VIH y el CMV para producir coinfección en el feto [2,3,8–10,23]. De hecho, en los casos en los que se produce transmisión vertical del VIH, la prevalencia de CMVc aumenta hasta el 26% [4,10]. Ambos virus pueden estimular la expresión de genes y la replicación viral de forma recíproca [9]. Por otra parte, Adachi *et al.* calculan un riesgo 5 veces mayor de transmisión de VIH si la madre presenta viruria de CMV [7]. Se conoce que el VIH tipo 2 presenta menores tasas de transmisión vertical que el VIH tipo 1, sin embargo no se ha estudiado qué serotipo de VIH se asocia con más frecuencia a la coinfección por CMV. Payne *et al.* anunciaron que la viremia de CMV en etapas precoces de la vida podría ser un predictor del reservorio viral de VIH tras la supresión virológica con antirretrovirales posiblemente por la coinfección de los mismos linfocitos de memoria [29].

Otras vías de transmisión perinatal o postnatal de CMV son a través de la lactancia materna o el contacto con secreciones vaginales en el momento del parto [30]. Estas vías implican un riesgo menor de morbilidad neurológica comparado con el CMVc aunque podría estar aumentado en niños con coinfección por VIH o en neonatos pretérminos, no obstante parece que el TAR parece disminuir dicho riesgo [21]. En países desarrollados la lactancia materna en hijos de madre VIH se encuentra desaconsejada, aunque es una vía a tener en cuenta en países en vías de desarrollo.

La principal limitación de este estudio es el reducido tamaño muestral. A pesar de ser un estudio retrospectivo, al obtener los datos de un protocolo asistencial de nuestro centro en el que se criba de rutina el CMV en muestra urinaria en todos los nacidos hijos de madre con VIH, contamos con todos los datos sin haber pérdida de éstos.

El adecuado control del VIH durante la gestación asociado a un buen estadio inmunológico, podría reducir la tasa de CMVc en hijos de madre con VIH, la cual había sido reportada en la era pre-TAR como muy superior a la de la población general.

En nuestra cohorte la prevalencia de CMVc en hijos de madre con infección por VIH podría estar próxima a la prevalencia de CMVc en la población general. No obstante, estudios con mayor tamaño muestral, multicéntricos y prospectivos deberían ser desarrollados para comprobar dicha prevalencia. De confirmarse

Tabla 4 **Datos clínicos de los neonatos expuestos al VIH.**

Total recién nacidos N = 69 (%)	N (%)	IC 95%
Edad gestacional		
Mediana	38,4 (37,5-39,1)*	
A término	59 (85.5%)	75,3-91,9%
Pretérmino	10 (14.5%)	8,1-24,7%
Extremo (< 28 SEG)	1/10 (10%)	1,8-4,0%
Muy prematuro (28-32 SEG)	0 (0%)	0,0-2,8%
Moderados-tardíos (32-37 SEG)	9/10 (90%)	59,6-98,2%
Sexo		
Mujeres	38 (55.1%)	43,4-66,2%
Varones	31 (44.9%)	33,8-56,6%
Antropometría		
Mediana percentil peso	39 (23-65)*	
Peso < p10	5 (7.2%)	3,1-15,9%
Peso > p90	4 (5.8%)	2,3-13,9%
Mediana percentil longitud	29 (12-55)*	
Longitud < p10	12 (17.4%)	10,2-27,9%
Longitud > p90	1 (1.4%)	0,3-7,8%
Mediana percentil PC	43 (24-67)*	
PC < p10	5 (7.2%)	3,1-15,9%
PC > p90	6 (8.7%)	4,1-17,7%
Síntomas compatibles con CMVc		
Exantema	0 (0%)	0,0-5,3%
Visceromegalia	0 (0%)	0,0-5,3%
Petequias	0 (0%)	0,0-5,3%
Neurológicos	0 (0%)	0,0-5,3%
Periodo neonatal		
Ingreso por prematuridad	10 (14.5%)	8,1-24,7%
Sepsis neonatal precoz	2 (2.9%)	0,8-9,9%
Analítica de sangre		
Leucocitos /mm^3	14.925 (11.700-18.900)*	
Plaquetas /mm^3	307.000 (261.000-353.000)*	
Plaquetas <100000/mm^3	0 (0%)	0,0-5,3%
Hb g/dl	15.9 (14.5-17)*	
Hb <15 g/dl	22/66 (33.3%)	23,2-45,3%
AST Elevada	38/50 (76%)	62,6-85,7%
AST U/L	75 (58-98)*	
AST Elevada	2/54 (3.7%)	1,0-12,5%
ALT U/L	93 (54-132)*	
GGT Elevada	24/65 (36.9%)	26,2-49,1%
GGT U/L	241 (192-275)*	
Bilirrubina total mg/dl	5.2 (4.3-6.4)*	
Bilirrubina directa mg/dl	0.39 (0.2-0.56)*	
Cribado auditivo		
Pasa bilateral OEAs	67 (97.1%)	90,0-99,2%
No pasa unilateral OEAs	1 (1.4%)	0,3-7,8%
PEAT	Normales	
No pasa bilateral OEAs	1 (1.4%)	0,3-7,8%
PEAT	pasa a 80 dB	
Transmisión vertical VIH	0 (0%)	0,0-5,3%
Citomegalovirus congénito	0 (0%)	0,0-5,3%

*Mediana (p25-75); CMVc: citomegalovirus congénito; PC: perímetro cefálico; < p10: menor de percentil 10 para edad gestacional y sexo (Estudio Español del crecimiento 2010); > p90: mayor de percentil 90 para edad gestacional y sexo (Estudio Español del crecimiento 2010); SEG: semanas de edad gestacional; PEAT: Potenciales evocados auditivos de tronco encefálico; OEAs: Otoemisiones acústicas.

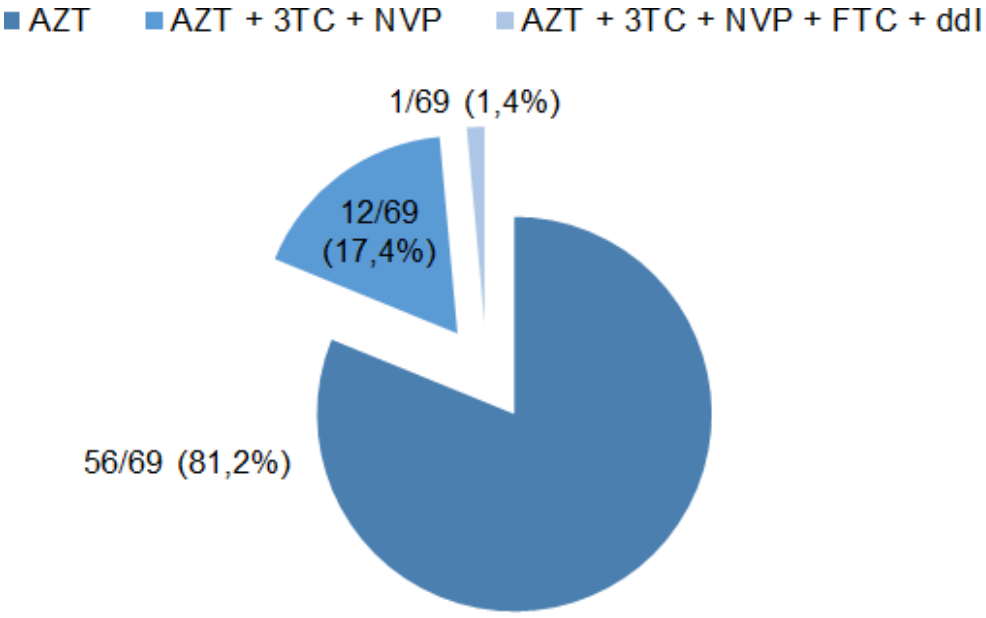

Figura 2 | **Profilaxis o tratamiento muy precoz del recién nacido expuesto al VIH**

3TC: Lamivudina; AZT: Ziduvudina; ddI: didanosina; FTC: emtricitabina; NVP: nevirapina.

estos hallazgos, las gestantes con infección por el VIH con buen control clínico, virológico e inmunológico y con TAR precoz en la gestación podrían reducir su grado de incertidumbre de cara al potencial riesgo de CMVc en su descendencia.

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CONFLICTOS DE INTERÉS

Los autores declaran no presentar conflictos de interés

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El código postal como "código de barras" de las resistencias antimicrobianas

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RESUMEN

Introducción. La necesidad de integrar en la práctica clínica las resistencias locales es cada vez más urgente, especialmente en Atención Primaria, donde el tratamiento empírico es frecuente.

Material y métodos. Se desarrolló un estudio retrospectivo observacional en el área de salud de Alcalá de Henares de los aislados microbiológicos positivos de *Neisseria gonorrhoeae* de cualquier localización (uretral, cervical, faríngea, rectal u orina). Se analizaron características sociodemográficas y resistencias a cefalosporinas, azitromicina, penicilina y quinolonas. Se relacionó cada aislado con su código postal de procedencia.

Resultados. Se analizaron 256 muestras microbiológicas de *N. gonorrhoeae*, la mayoría pertenecientes a hombres (92,9%) con edad media de 33 años. La mitad de las muestras (49,8%) fueron resistentes a ciprofloxacino. La evolución temporo-espacial de las resistencias antimicrobianas se integró en mapas de calor con los códigos postales con más resistencias

Conclusión. Conocer las resistencias locales puede ayudar a pautar tratamientos empíricos más adecuados, especialmente en Atención Primaria, evitando la utilización de antibióticos inadecuados y disminuyendo las tasas de resistencias.

Palabras clave: *Neisseria gonorrhoeae*; Resistencia antimicrobiana, Bacteria, Determinantes sociales de la salud

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The postal code as a "bar code" of antimicrobial resistance

ABSTRACT

Introduction. The need to integrate local resistances into clinical practice is increasingly urgent, especially in Primary Care where empirical treatment is frequent.

Methods. A retrospective observational study of positive microbiological isolates of *Neisseria gonorrhoeae* from any location (urethral, cervical, pharyngeal, rectal or urine) was carried out in the health area of Alcalá de Henares. Sociodemographic characteristics and resistance to cephalosporins, azithromycin, penicillin and quinolones were analyzed. Each isolate was related to its postal code of origin.

Results. We analyzed 256 microbiological samples of *N. gonorrhoeae*, most of them male (92.9%) with a mean age of 33 years. Half of the samples (49.8%) were resistant to ciprofloxacin. Temporal and spatial evolution of antimicrobial resistance was integrated in heat maps.

Conclusion: Knowing local resistances can help to prescribe more adequate empirical treatments, especially in Primary Care, avoiding inadequate antibiotics and decreasing resistance rates.

Keywords: *Neisseria gonorrhoeae*; Drug Resistance, Bacterial, Social Determinants of Health

INTRODUCCIÓN

La interacción entre los determinantes sociales, entendidos como condiciones de vida, y la salud es de sobra conocida, especialmente en relación con la calidad de vida y longevidad [1,2]. De hecho, en un editorial sobre este tema titulado "Tu código postal puede modificar tu código genético"[3] se explican las intersecciones entre salud, condiciones de vida, biología y conducta y resultados de salud, donde podemos englobar también el

término "epigenética". Si hablamos de enfermedades infecciosas, su relación con las condiciones de vida y salubridad en muchas ocasiones es más que evidente, incluyendo también la vacunación en este punto (entre ellas la vacuna del SARS-CoV-2) [4,5]. Sin embargo, existe aún poca evidencia sobre cómo se relacionan los determinantes sociales y las resistencias antimicrobianas, especialmente a pequeña escala. Resulta además interesante que, con el auge de las resistencias antimicrobianas, que constituyen una amenaza para la salud global, las resistencias a pequeña escala en el ámbito de trabajo habitual no están contempladas en la mayoría de los protocolos o guías clínicas [6]. Esto, sumado a los tiempos de respuesta sobre todo en algunos ámbitos (especialmente en Atención Primaria, más largos que en otros niveles asistenciales) y a la aún escasa disponibilidad de test de resistencias rápidos en la práctica clínica diaria facilitan la prescripción de antimicrobianos con incertidumbre, y en muchas ocasiones de forma empírica. El objetivo "test and treat" se complica en algunas enfermedades donde las resistencias antimicrobianas constituyen un verdadero problema. Un claro ejemplo es la infección por *Neisseria gonorrhoeae*, una de las infecciones de transmisión sexual (ITS) más prevalentes en nuestra zona y en la que está aumentando la resistencia antimicrobiana a los tratamientos habituales. Teniendo en cuenta todas estas premisas se llevó a cabo un estudio con el objetivo de realizar un análisis geoespacial de la infección por *N. gonorrhoeae* resistente durante los últimos cinco años (2016-2021).

MATERIAL Y MÉTODOS

Diseño, población y variables. Se realizó un estudio descriptivo en nuestra área de salud para estimar la frecuencia de las resistencias a los antimicrobianos y su distribución temporal de los aislados de *N. gonorrhoeae* durante 5 años (desde 2016 hasta octubre de 2021). Se utilizó como definición de caso el diagnóstico microbiológico de infección por *N. gonorrhoeae* mediante cultivo positivo (recomendaciones del Comité Europeo de Susceptibilidad a los Antimicrobianos (EUCAST) [7]. Se incluyeron todas las muestras microbiológicas con cultivo positivo remitidas a nuestro laboratorio de microbiología procedentes de pacientes con sospecha de ITS de diferentes fuentes: citología, exudados uretrales, endocervicales, rectales, faríngeos y orina.

Se recogieron las siguientes variables: a) datos sociodemográficos (sexo y edad); b) datos clínicos (servicio médico de origen del paciente, localización) c) variables de resultado (resistencia a los antimicrobianos más utilizados (azitromicina, cefalosporinas de tercera generación, ciprofloxacino y amoxicilina). Se aplicaron medidas de geolocalización mediante código postal asociado de todos los aislados de *N. gonorrhoeae* desde 2016 y se visualizaron las áreas geográficas con prevalencia de resistencia a diferentes antimicrobianos a través de mapas de códigos postales en una base de datos anónima de muestras de *N. gonorrhoeae*.

Análisis estadístico. Se realizó una descripción de los casos diagnosticados de *N. gonorrhoeae* mediante medidas de tendencia central y dispersión para las variables cuantitativas, así como distribuciones de frecuencias y porcentajes para las variables cuantitativas y cualitativas, respectivamente.

Las proporciones de resistencia global por distrito se compararon mediante pruebas de contraste de hipótesis Chi cuadrado, con corrección exacta de Fisher para celdas inferiores a 5, y se representó gráficamente la evolución temporal de las resistencias durante los últimos 5 años. Se llevó a cabo un análisis espacial mediante el empleo de datos agregados de muestras pertenecientes a los códigos postales del área estudiada, por año (número de casos de infección por *N. gonorrhoeae* resistentes a cefotaxima, azitromicina, amoxicilina y quinolonas). Se utilizó el código postal asociado de cada paciente individual) y los resultados se visualizaron mediante el empleo de mapas de calor, tanto para resistencia global como para cada uno de los antibióticos de forma independiente.

El estudio se realizó de acuerdo con los principios de la última revisión de la Declaración de Helsinki. Asimismo, se siguieron las normas internacionales para la realización de estudios epidemiológicos, recogidas en la Guía Internacional para la Revisión Ética de Estudios Epidemiológicos [8]. El estudio fue aprobado por el Comité de Ética del Hospital Universitario Príncipe de Asturias (número de protocolo: IE ETS).

RESULTADOS

Durante los casi seis años de estudio, se incluyeron 256 muestras microbiológicas procedentes de distintas localizaciones y correspondientes a pacientes individuales. En esta población se detectaron un total de 159 muestras con al menos un mecanismo de resistencia a antimicrobianos, lo que representa una prevalencia global del 59,4%. Las características de la muestra se encuentran en la Tabla 1. La mayoría de los pacientes eran hombres (92,9%), con una edad media en la fecha de diagnóstico de 33 años (desviación estándar: 9,4, rango: 18-66). La mayoría de las muestras microbiológicas se obtuvieron en servicios hospitalarios con casi un 30% de las muestras procedentes de Atención Primaria. Estratificando por antibiótico, las resistencias más frecuentes fueron a ciprofloxacino (49,8%) seguidas de amoxicilina (16,8%) y azitromicina (13,8%).

El estudio espacial de la muestra se realizó utilizando datos agregados de muestras pertenecientes a los códigos postales del área estudiada, por año (número de casos de infección por *N. gonorrhoeae* resistentes a cefotaxima, azitromicina, amoxicilina y quinolonas). Se utilizó el código postal asociado a la muestra clínica.

Al comparar los distritos con mayor número de muestras se observó un rango muy variable de resistencia, con proporciones que oscilaron desde el 1,6% de las muestras hasta el 24,2%, aunque estas diferencias no alcanzaron valores de significación estadística (Tabla 2).

Posteriormente se visualizó mediante mapas de calor los códigos postales donde se encontraban el grueso de muestras y se asoció un color en función del número de casos resistentes (Figura 1). Se realizó un mapa de las resistencias totales (re-

Tabla 1 Descripción de la muestra

Datos sociodemográficos	N	
Edad (media ± DE)	256	33 ± 9
Sexo hombre; n (%)	256	238 (92,9%)
Servicio peticionario, n (%)	256	
Dermatología		78 (30,5%)
Atención Primaria		71 (27,7%)
Urología		50 (19,5%)
Urgencias		29 (11,3%)
Medicina Interna		13(5,1%)
Otros		10 (3,9%)
Ginecología		5 (1,9%)
Año de la muestra positiva; n (%)	256	
2016		29 (11,3%)
2017		49 (19,1%)
2018		59 (23,0%)
2019		50 (19,5%)
2020		33 (12,9%)
2021		36 (14,1%)
Resistencia global al menos 1 antimicrobiano; n (%)	256	152 (59,4%)
Resistente a ciprofloxacino		127 (49,8%)
Resistente a amoxicilina		43 (16,8%)
Resistente a azitromicina		35 (13,8%)
Resistente a cefotaxima		3 (1,2%)

Tabla 2 Proporción de resistencias por distrito

Código postal	No resistencia n (%)	Resistencia n (%)	Valor p
28800	5 (6,1%)	2 (1,6%)	
28801	2 (2,4%)	2 (1,6%)	
28802	12 (14,6%)	20 (16,3%)	
28803	14 (17,1%)	16 (12,9%)	
28804	10 (12,2%)	18 (14,5%)	0,664
28805	13 (15.8%)	27 (21,8%)	
28806	19 (23,2%)	30 (24,2%)	
28807	7 (8,5%)	9 (7,3%)	
Total	82	124	

sistencia al menos a un antibiótico (Figura 1a)), y de las resistencias a cada antibiótico de forma independiente (Figura 1b resistencias a cefotaxima; Figura 1c resistencias a penicilina; Figura 1d resistencias a azitromicina y Figura 1e resistencias a ciprofloxacino).

En la figura 2 se muestra una distribución de las resistencias por año, pudiendo observarse una tendencia ascendente de las resistencias de forma global.

DISCUSION

Los resultados de nuestro estudio muestran una resistencia global de *N. gonorrhoeae* en las cepas testadas del 59,4%, con una relación temporal de aumento de resistencias a ciprofloxacino y penicilina claramente mayor en los dos últimos años.

Las tasas de resistencias a ciprofloxacino de nuestro estudio son levemente mayores que en otras series realizadas a nivel nacional, donde describen tasas de resistencia de ciprofloxacino en torno a un 50% [9-11]. Sin embargo, en otros estudios realizados a nivel mundial las tasas de resistencias son bastante más elevadas [12-14]. En cuanto a cefalosporinas, nuestra tasa de resistencia en las muestras analizadas se halla en torno a un 1,1%, lo que puede estar en consonancia con las series mencionadas previamente [15], pero claramente inferior a la serie de Fuertes Vega et al [16]. Esto podría hacernos concluir que de momento el uso de ceftriaxona como tratamiento de la infección por *N. gonorrhoeae* es el adecuado en nuestro medio. Cabe resaltar que en el estudio de las ITS la biología molecular y la utilización de técnicas de secuenciación para identificar cepas es cada vez más frecuente [12,17], especialmente en grandes ciudades y a nivel hospitalario, es decir, a gran escala. Además, hay que sumar a esto que el control de las ITS es sumamente complejo por múltiples factores, entre los que intervienen el estigma, desconocimiento, movilidad a otros centros sanitarios y la dificultad de realizar estudios de contacto óptimos. Queda por tanto incertidumbre sobre qué medidas podemos implementar en la práctica clínica diaria para poder predecir de una forma más ajustada las resistencias antimicrobianas de *N. gonorrhoeae*. Tras visualizar por códigos postales los aislamientos resistentes (global y estratificados por tipo de antibióticos) podemos deducir rápidamente en qué zonas se encuentran las cepas resistentes y cómo se agrupan en el tiempo. A pesar de que aún no hay evidencia para poder establecer correlaciones entre estos datos, el hecho de conocer las resistencias a nivel local nos puede ayudar a pautar tratamientos empíricos más adecuados, evitando la sobreexposición a antibióticos resistentes. Es decir, utilizar el código postal del paciente como herramienta para predecir el éxito o fracaso de un tratamiento antibiótico ("dime tu código postal y te diré tus resistencias antimicrobianas").

Nuestro estudio presenta algunas limitaciones, entre las que podemos destacar la posibilidad de discrepancias entre código postal recogido en la historia clínica y el real, y la ausencia de conocimiento sobre el tratamiento empírico recibido, dado que no está recogido en la historia clínica en muchos pacientes.

Por último, tras la pandemia por SARS-CoV-2, que ha evi-

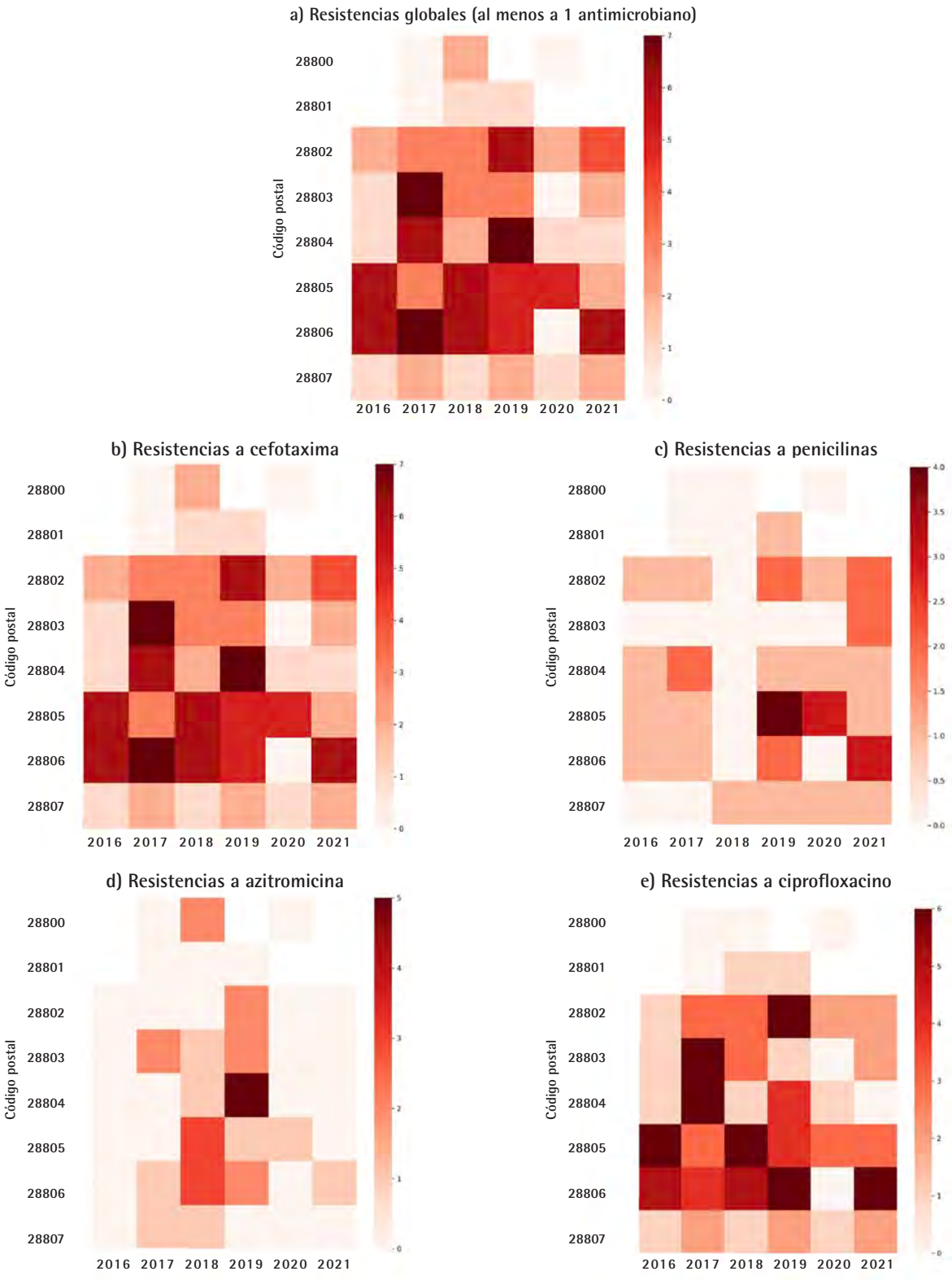

Figura 1 | Evolución geoespacial de los aislados de *N. gonorrhoeae* resistentes por código postal y por año

En eje de abscisas: evolución temporal; En eje de ordenadas: código postal asociado. A la derecha se observa la línea de calor con la densidad de casos por código postal.

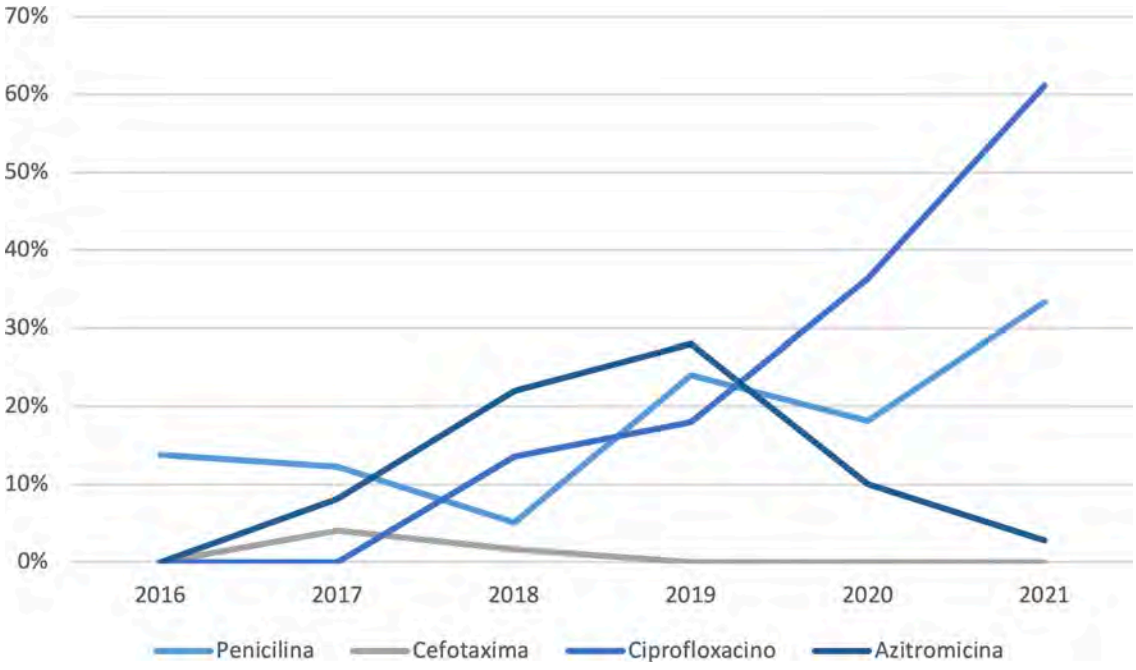

Figura 2 | **Evolución de la resistencia antimicrobiana de los aislados de *N. gonorrhoeae* (2016-2021)**

denciado todo un cambio de paradigma en la forma de entender la medicina, y ante el auge de herramientas de geolocalización como medida epidemiológica creemos que conocer las resistencias locales actualizadas y a muy pequeña escala puede ser una herramienta muy útil de salud pública.

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CONFLICTOS DE INTERÉS

Los autores no declaran conflictos de interés

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Carta al Director

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Osteomielitis polimicrobiana en extremidad de la mano tras mordedura de gato

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Estimado Editor: La osteomielitis secundaria a mordedura de gato es una complicación poco frecuente, pero que puede tener consecuencias graves. Presentamos un caso de osteomielitis polimicrobiana en un dedo de la mano, tras mordedura de gato, producido por *Fusobacterium russii*, *Actinomyces odontolyticus* y *Actinomyces canis*. Presentamos el primer caso documentado de osteomielitis en el que se encuentra implicado *F. russi*.

Varón de 82 años con antecedentes personales de diabetes mellitus tipo II e hipertensión arterial a tratamiento. Remitido desde atención primaria por herida sobreinfectada en el 2º dedo de la mano izquierda de 1 mes de evolución, tras mordedura de gato. Se trató secuencialmente por mala evolución con ciprofloxacino 6 días, cefuroxima 4 días y moxifloxacino 6 días. En la exploración física se observaron 3 heridas sangrantes con supuración purulenta, dolor y signos de inflamación sin acompañamiento de fiebre (Figura 1a). En el estudio de laboratorio presentó niveles de proteína C-reactiva 5,2 g/dl y la radiografía de la mano izquierda demostró imágenes de lesiones líticas a nivel de la falange distal y media compatibles con osteomielitis (Figura 1d).

Al ingreso se realizó drenaje de la herida con cultivo microbiológico negativo tanto para bacterias como para hongos. A los 7 días se realizó nueva radiografía, evidenciando avance de osteomielitis (Figura 1e). Tras 10 días desde el ingreso se realizó amputación de la falange distal y media del 2º dedo de la mano izquierda, enviando una muestra ósea a microbiología. La tinción de gram evidenció una alta presencia de leucocitos polimorfonucleares sin observación de microorganismos. En el cultivo bacteriológico se identificaron tres microorganismos (*A. odontolyticus, A. canis y F. russii* (Figuras 1b y 1c)) mediante espectrometría de masas (MALDI-TOF MS, bioMérieux). El estudio de sensibilidad se realizó mediante tiras de E-test (bioMérieux). *A. odontolyticus* y *A. canis* mostraron CMI a penicilina de 0,094; *F. russi*, presentó sensibilidad a metronidazol (CMI 0,032 mg/L) y clindamicina (CMI 0,032 mg/L) y resistencia a amoxicilina-clavulánico (CMI>32 mg/L) según criterios EUCAST 2021.

El tratamiento empírico al ingreso fue ceftriaxona iv (2000mg/24h) y clindamicina iv (600mg/8h) durante 3 días, al 4º día se cambió ceftriaxona por amoxicilina-clavulánico iv (2000/200mg/8h) y se continuó con clindamicina iv. A los 10 días tras la amputación se pautó amoxicilina-clavulánico iv (2000/200mg/8h) más clindamicina iv (600mg/8h). La evolución del paciente fue favorable y se le dio el alta pasados 7 días desde la amputación con amoxicilina-clavulánico oral (875/125mg/8h). Tras los resultados microbiológicos (6 días después del alta) se añadió clindamicina oral (300mg/8h) durante 7 días, manteniendo amoxicilina-clavulánico 20 días más. El tiempo de tratamiento tras la amputación fue de 33 días con resolución total de la infección.

F. russi y *A. canis* son microorganismos anaerobios, cuya recuperación en cultivo puede tardar entre 5-14 días, que se encuentran específicamente en la cavidad oral de gatos y perros, raramente encontrados en infecciones humanas [1-3]. El tratamiento indicado en casos de mordedura de animales es un antimicrobiano eficaz contra bacterias aerobias y anaerobias, como amoxicilina-clavulánico [4-6].

Hay que tener en cuenta factores de riesgo, como la diabetes, y comenzar rápidamente un tratamiento empírico adecuado, para evitar el progreso de la infección hacia el hueso [5].

Es relevante la capacidad de identificar nuevas especies de anaerobios debido a la incorporación de la espectrometría de masas (MALDI-TOF), permitiendo conocer otros agentes que pueden contribuir a una peor evolución en base a sus características patógenas y de sensibilidad [7], como se observa en el *F. russi* aislado en este paciente que era resistente a amoxicilina-clavulánico.

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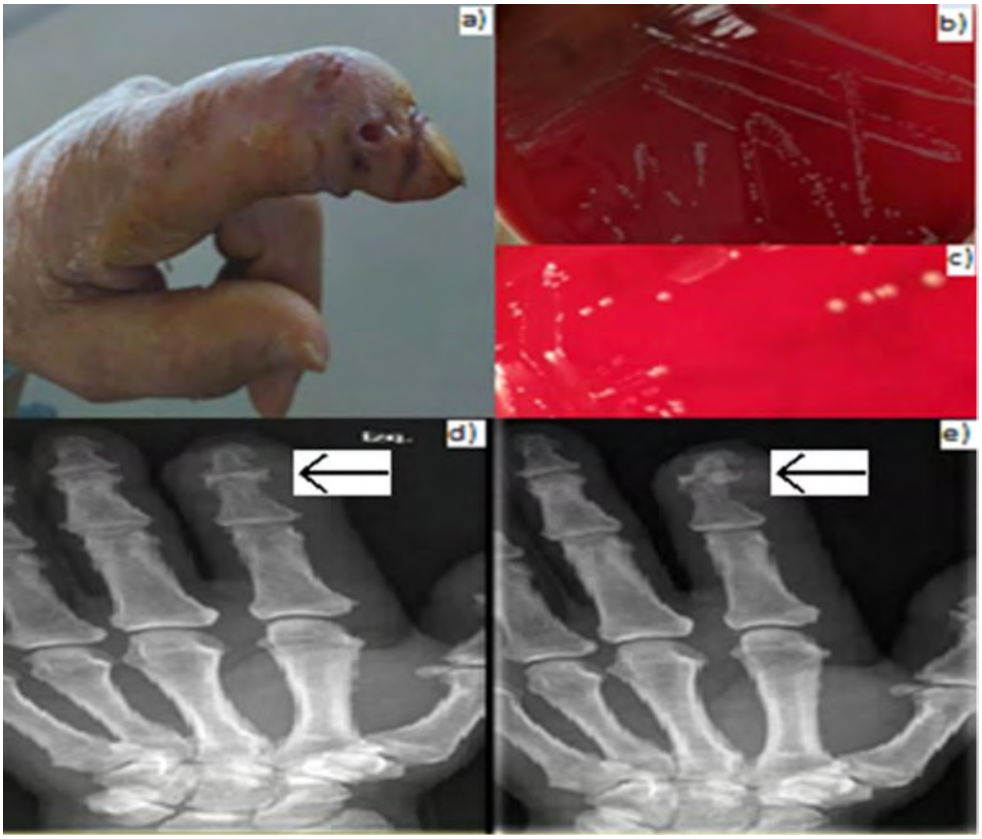

Figura 1 | **a) Herida 2º dedo mano izquierda. b) Colonia *A. canis*. c) Colonia *F. russii*. d) Radiografía mano izquierda al ingreso. e) Radiografía mano izquierda tras 7 días ingreso**

Las mordeduras de gato que presentan una evolución tórpida o un tratamiento inadecuado, pueden derivar en una afectación ósea que en ocasiones únicamente se resuelve con la amputación. Un manejo empírico adecuado y un diagnóstico etiológico precoz son determinantes para un correcto abordaje de estos casos.

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CONFLICTOS DE INTERÉS

Los autores declaran no presentar conflictos de interés

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Letter to the Editor

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Congenital tuberculosis in a premature newborn

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Sir,

According to the World Health Organization, tuberculosis (TB) is among the ten leading causes of mortality and the first etiology of infectious diseases globally [1,2]. The congenital form is an infrequent presentation of TB (only 300 cases have been reported in the English literature [3]), and it occurs in newborns of mothers who develop active disease during pregnancy or have silent genital TB [3].

The most frequent TB clinical form in pregnant women is extrapulmonary, and it is very difficult to diagnose due to the high variability of symptoms [3]. In newborns, it may present nonspecific clinical manifestations such as irritability, fever, cough, respiratory distress, hepatosplenomegaly, lymphadenopathy, and abdominal distension [3].

We present a congenital TB case in a female newborn to a dichorionic diamniotic twin gestation, who was admitted to the pediatric ICU due to severe respiratory distress and prematurity. Bronchopneumonia of possible fungal etiology was suspected to be the cause of the distress, as chest X-rays (Figure 1) showed bilateral infiltrates. Chest computerized tomography (CT) scans (Figure 2) reported areas of pulmonary consolidation and hepatosplenomegaly.

Treatment started with ceftazidime (33 mg/kg/8h) and vancomycin (15 mg/kg/6h). As there was no clinical improvement, treatment was changed to meropenem (20 mg/kg/8h), azithromycin (20 mg/kg/day), cotrimoxazole (10/50 mg/8h), and fluconazole (12 mg/day). Persistent polypnea continued, so fluconazole was substituted for amphotericin B (5 mg/kg/day) and caspofungin (2 mg/day). Despite respiratory support and empiric broad-spectrum antimicrobial therapy, she did not respond adequately.

After that, hemophagocytic syndrome (HPS) was suspected as it met six of the eight criteria described by the Spanish Association of Pediatrics (AEPED) [4] for its diagnosis, namely: prolonged fever, hepatosplenomegaly, cytopenias (anemia, thrombocytopenia, and leukopenia), hyperferritinemia (2,129-3,212 ng/mL), hypofibrinogenemia (83 mg/dL) and elevated soluble CD25 (470 µL).

The first bronchoalveolar lavage's auramine stain was negative, but at 14 incubation days, MGIT culture and the confirmatory Ziehl-Neelsen stain were positive for *Mycobacterium tuberculosis*. IGRA was not performed as the patient was a newborn. Neonatal anti-tuberculous treatment was started (according to the 2016 SEIP consensus [5]) with isoniazid (15 mg/kg/day), rifampicin (20 mg/kg/day), pyrazinamide (35 mg/kg/day) and amikacin (15 mg/kg/day). She developed hepatotoxicity, so pyrazinamide was changed to levofloxacin (7.5 mg/kg/day), as it is a second-line anti-tuberculous drug and because of its good diffusion to the central nervous system [6]. The patient had complicated hepatosplenomegaly with hepatic and splenic microabscesses, which evolved into calcified granulomas [evidenced by abdominal ultrasound (Figure 2)]. On the other hand, HPS resolved spontaneously when TB was treated.

The patient's twin sister was born healthy. The mother, a 37-year-old Moroccan woman, was asymptomatic and apparently without any clinical background of interest. IGRA was not performed beforehand as the parents reported that it was done in a private clinic, and it was negative. No abnormalities were seen in the chest X-ray, and the sputum's Ziehl-Neelsen stain and cultures were negative. The endometrial aspirate culture was positive for *M. tuberculosis*, so she also started treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol.

The patient completed 1-year oral maintenance anti-tuberculous treatment with isoniazid (90 mg/day), rifampicin (90 mg/day), and pyridoxine (12.5 mg/day) with good response. A contact study was not performed as the parents were asymptomatic, and it was suspected that the mother had a disseminated TB years before.

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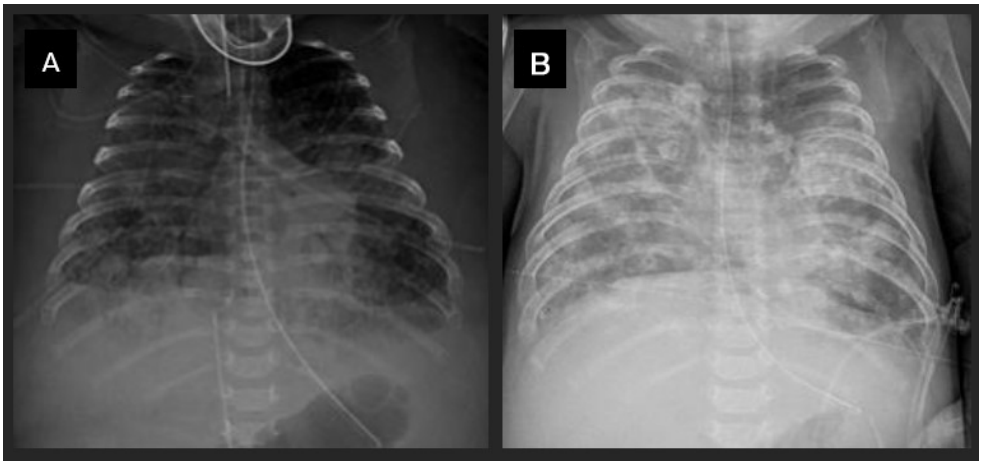

Figure 1 | **Chest X-ray at birth (A): Bilateral infiltrates, predominantly in the right lung. Chest X-ray at 60 days (B): Pulmonary nodules consistent with miliary tuberculosis.**

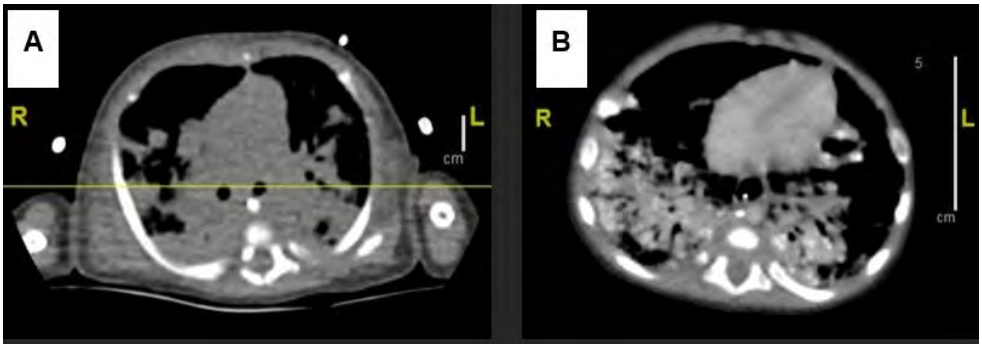

Figure 2 | **Chest CT at birth (A): Diffuse patchy nodular images of consolidation in both lung fields that coalesce to form larger areas of consolidation with air bronchogram. In LIL there is a zone in the area of greatest consolidation that could suggest the beginning of pulmonary cavitation; and 60 days later (B): Pulmonary granulomas, cavitations in the left lung and hilar and mediastinal adenopathies.**

TB continues to be a global public health problem and approaching its diagnosis to pregnant women and their newborns represents a daunting challenge for clinicians. An exhaustive epidemiological background study is crucial to firstly establish a high level of suspicion, and secondly integrate this pathology into the differential diagnoses of multiple clinical conditions that are observed in pregnant women and newborns.

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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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Two rare cases of pleural infection due to *Prevotella* species

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Sir,

Prevotella species are anaerobic bacteria that form part of the oral microbiota and upper respiratory and genitourinary tracts. They are usually associated with oral infections, but it can be also observed in some other infections such as skin and soft tissue, and pleuropulmonary infections. Until now, there are only few reports on pleural infection published in the literature caused by *Prevotella* species and obtained in pure culture [1-7]. We here present two additional and uncommon cases of pleural infection caused by *Prevotella* species and a review of the cases previously published.

Case 1.- A 60-year-old man was admitted due to chest pain, general malaise and vomiting. Blood analysis showed increased levels of glucose (198 mg/dL), urea (200 mg/dL), creatinine (1.53 mg7dL), procalcitonin (65.26 ng/mL), AST (437 U/L), and ALT (308 U/L). A physical exam showed cervical edema, and a cervico-thoracic CT scan showed great quantity of gas affecting cervical region and mediastinum (Figure 1) along with a pleural effusion. A diagnosis of mediastinitis was established and a thoracotomy was performed along with drainage of pleural effusion as well. Treatment with piperacillin-tazobactam and linezolid was started.

Case 2.- A 47-year-old woman was admitted due to drowsiness and inability to emit language and open the eyes. Blood analysis showed increased levels of glucose (150 mg/dL), sodium (105 mEq/L), C-reactive protein (42.7 mg/L) and decreased levels of potassium (3.10 mEq/L), chlorine (80 mEq/L) and white cell count (3.44 x 10^3/mm^3). A brain CT scan was performed showing no abnormalities. The patient was admitted to the ICU and treatment with fluid and electrolyte replacement was initiated. A hormonal study was performed showing increased levels of TSH (31.59), antibodies anti-peroxidase (>1000 UI/mL) and decreased levels of thyroxine (<0.28 ng/dL). Moreover, the antinuclear antibodies were positives. The patient was diagnosed of systemic lupus erythematosus and myxedematous coma. Later, a chest ultrasound revealed a left pleural effusion; drainage was then performed.

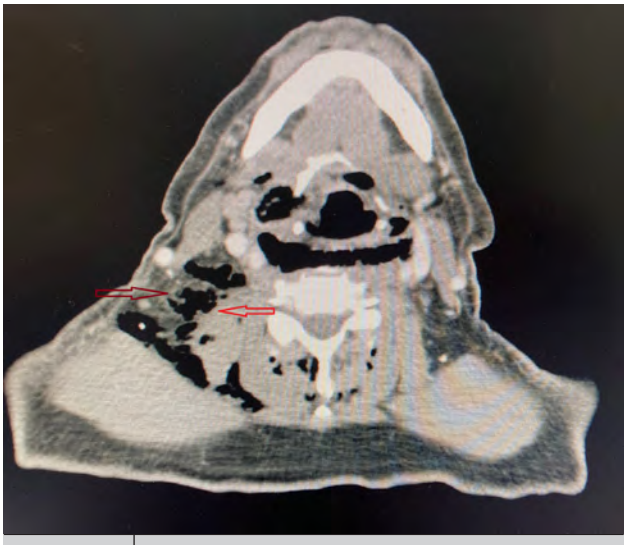

Figure 1 | **Cervical CT scan showing a big quantity of gas corresponding to a mediastinitis.**

Both pleural fluids were sent to the microbiology laboratory for culture. The two samples were inoculated onto both aerobic and anaerobic blood agar (Becton Dickinson), chocolate agar (Becton Dickinson), and thioglycolate broth (Becton Dickinson), incubating all media at 37º C for 5 days. Gram staining of both fluids exhibited abundant Gram-negative rods. On the second day of incubation, numerous

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Table 1 **Main characteristics of *Prevotella* pleural infections.**

Case (year of publication) [reference]	Age (years)/ sex	*Prevotella* species	Identification method	Underlying conditions and/or risk factors	Possible source of infection	Clinical manifestations	CRP (mg/L)	Treatment	Outcome
1 (2013) [2]	17/M	*Prevotella* spp	PCR (16S rRNA)	NR	NR	Fever, cough, chest pain	NR	Antibiotics + drainage	Cure
2 (2015) [5]	76/M	*Prevotella* spp	PCR (16S rRNA)	DM	NR	Fever, chest pain	147.4	Antibiotics + drainage	Cure
3 (2018) [3]	88/M	*Prevotella dentalis*	MALDI-TOF MS PCR (16S rRNA)	CRD DM	Lung	Chronic pleural effusion	194.1	Antibiotics + drainage	Died
4 (2020) [5]	42/M	*Prevotella* oris	NR	DM	Lung	Chest pain, left upper limb weakness, cough	399	Antibiotics + drainage	Cure
5 (2021) [6]	12/M	*Prevotella pleuritidis*	Next-generation sequencing-based clinical metagenomics	DM	Lung	Fever, cough, chest pain, dyspnea	NR	Antibiotics + drainage	Cure
6 (2021) [7]	49/M	*Prevotella* spp	PCR (16S rRNA)	NR	Lung	Asthenia, fever, weight loss, dyspnea	87.5	Antibiotics + thoracoscopic surgery	Cure
7 (2022) [PR]	60/M	*Prevotella* oris	MALDI-TOF MS PCR (16S rRNA)	Mediastinitis	Lung	Chest pain, general malaise, vomiting	Normal	Antibiotics + drainage	Died
8 (2022) [PR]	47/F	*Prevotella denticola*	MALDI-TOF MS PCR (16S rRNA)	Autoimmune disease	NR	Drowsiness, inhability to emit language	42.7	Antibiotics + drainage	Cure

M: male; F: female; NR: not reported; CRP: C-reactive protein; PR: present report; DM: diabetes mellitus; CRD: chronic respiratory disease.

colonies of microorganisms were observed in pure culture on anaerobic blood agar alone in both samples. MALDI-TOF MS (Bruker Biotyper, Billerica, MA) results identified the strains as *P. oris* and *P. denticola* (log scores of 2.20 in case 1 and 2.14 in case 2). Biotyper software version 9 was used (8468 msp) for analyses. The two strains were sent to the Centre of Genomic and Oncologic Research (GENYO, Granada, Spain) for 16S rRNA gene sequence analysis using a previously reported method [8]. Fragments of 1,363 bp (case 1) and 1,357 bp (case 2) were obtained. The strain from case 1 showed 99.42% similarity with the *P. oris strain* NCTC 13071 GenBank sequence (accession nº LR134384.1) and the strain from case 2, 99.2% similarity with the *P. denticola* strain SEQ210 17855 GenBank sequence (accession nº JN867285.1). 16S rRNA gene sequences of the isolates were submitted to GenBank (accession number OM909079 for case 1 and ON248549 for case 2).

The gradient diffusion strip method (Etest bioMérieux) was used for antimicrobial susceptibility testing based on 2022 EUCAST criteria [9]. MIC values for the strain isolated in case 1 were benzylpenicillin (0.125 mg/L), piperacillin-tazobactam (<0.016 mg/L), clindamycin (0.047 mg/L), meropenem (0.012 mg/L), and metronidazole (0.19 mg/L). Values for the strain isolated in case 2 were benzylpenicillin (8 mg/L), piperacillin-tazobactam (0.032 mg/L), clindamycin (>256 mg/L), meropenem (0.047 mg/L), and metronidazole (1 mg/L). In case 1, the patient rapidly developed to septic shock and dead after 6 days. In case 2, the patient was prescribed i.v. meropenem (500 mg/8 h) for 20 days and was discharged after 40 days.

Pleural infections caused by anaerobic bacteria are usually of polymicrobial nature, presented as mixed infections containing aerobes and anaerobes. We here reported two cases of pleural infection due to *P. oris* and *P. denticola* in pure culture. Table 1 shows the main characteristics of patients with pleural infections due to *Prevotella* spp.

The introduction of MALDI-TOF MS for routine analyses in clinical laboratories has improved the identification of anaerobic bacteria and may help to detect new species. Last years, antimicrobial resistance is increasing among anaerobic bacteria worldwide. *Prevotella* species have been traditionally considered susceptible to penicillin, but an increasing rate of resistance to this drug has been documented over recent years, ranging from 33% to 60%, especially in *P. bivia* [10,11]. Thus, empirical treatment with penicillin cannot be recommended in infections caused by *Prevotella* species. Regarding to metronidazole, some studies reported resistance of some *Prevotella* strains to this drug [12,13]. The above findings indicate that *Prevotella* species cannot be considered as usually susceptible to antibiotics. Antimicrobial resistance of *Prevotella* spp. and other anaerobes is an emerging problem that warrants closer antimicrobial surveillance, increased resistance testing, and the stringent monitoring of treatment failures.

This is a report of two additional cases of *P. oris* and *P. denticola* as cause of pleural effusion and indicates that *Prevotella* species can produce infections in pure culture at this location. These case reports and recent observations of

antimicrobial resistance among *Prevotella* species highlight the need for caution when treating these infections with antibiotics and for the susceptibility testing of Gram-negative anaerobes in all cases.

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Authors declare no conflict of interest.

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Carta al Director

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Osteomielitis del cuboides por *Mycobacterium smegmatis*

Hospital Universitario Juan Ramón Jiménez, Huelva, Spain.

Article history
Received: 4 May 2022; Revision Requested: 2 June 2022; Revision Received: 7 June 2022; Accepted: 14 June 2022; Published: 18 July 2022

Estimado Editor: *Mycobacterium smegmatis* es una micobacteria no tuberculosa de crecimiento rápido y escotocromógena, descrita por primera vez en 1884 en un chancro sifilítico y, un año después, en muestras de secreciones genitales normales [1], aunque hasta 1986 no se reconoció como patógeno humano [2]. Actualmente el grupo *Mycobacterium smegmatis* se compone de *M. smegmatis* sensu stricto, *M. wolinskyi y M. goodii* [3] Las micobacterias ambientales forman biofilms en las redes de agua urbanas, encontrándose también en el suelo, vegetación y animales [4]. Estas micobacterias tienen como mecanismo patogénico una inflamación granulomatosa con destrucción del tejido.

Presentamos un caso de osteomielitis del cuboides tras un pinchazo con un clavo. Se trata de un varón de 42 años sin antecedentes de interés que acude en varias ocasiones a urgencias por dolor e inflamación en el lateral externo del pie izquierdo y fiebre superior a 38ºC. Había sido tratado con cefadroxilo (500 mg/12h) y amoxicilina-clavulánico (875/125 mg/8h) por vía oral sin experimentar una respuesta favorable. El paciente refirió un traumatismo con un clavo un mes antes del inicio de los síntomas.

Tras dos semanas de tratamiento ambulatorio con los antibióticos mencionados, y debido el empeoramiento del cuadro clínico, el paciente acude de nuevo a urgencias donde se realiza un TAC, que muestra hallazgos compatibles con una osteomielitis aguda del cuboides con formación de absceso intraóseo y afectación de las partes blandas circundantes. Se decide ingresar al paciente e incrementar la dosis de amoxicilina-clavulánico a dosis de 2 g/8h.

Tras 10 días de ingreso y falta de respuesta al tratamiento, se interviene desbridamiento quirúrgico y se toman 5 muestras que se envían al laboratorio, donde se homogenizan y se siembran en placas de agar sangre, agar chocolate, agar McConkey; las cuales se incuban en atmósfera aerobia con enriquecimiento en CO_2, y en agar Schaedler y agar Kanamicina-Vancomicina, que se incuban en atmósfera anaerobia. En todas las muestras se aisló, a las 72 horas de incubación, *M. smegmatis*, identificado mediante MALDI-TOF con un score superior a 2,0. La cepa se envió al Centro de Referencia del Hospital Universitario Reina Sofía de Córdoba para realización de antibiograma mediante la técnica de microdilución en caldo. Según criterios CLSI [5] para micobacterias de crecimiento rápido, esta cepa fue resistente a ceftriaxona, cefepima, claritromicina y minociclina y sensible a aminoglucósidos (tobramicina, amikacina) quinolonas (moxifloxacino, ciprofloxacino), imipenem, linezolid, doxiciclina y cotrimoxazol.

Tras los resultados de los cultivos microbiológicos, la antibioterapia del paciente se sustituyó por una combinación de doxiciclina 100mg/12 horas, ciprofloxacino 750 mg/12 horas y cotrimoxazol 800/160 mg /8 horas.

El paciente presentó una buena evolución clínica (Figura 1) y toleró la deambulación, por lo que se pudo continuar el tratamiento ambulatorio tras 10 días de hospitalización. Se mantuvo el tratamiento final de doxiciclina; ciprofloxacino y cotrimoxazol a las mismas dosis ya pautadas en el ingreso durante 6 semanas.

Aunque *M. smegmatis* se ha descrito como causante de neumonía en pacientes con enfermedades de base [6,7] y en bacteriemias relacionada con catéter [8], estos casos son muy infrecuentes y produce, principalmente, infecciones de piel y tejidos blandos; por inoculación accidental por traumatismos, como pinchazos con espinas de plantas, o por cirugías y productos sanitarios contaminados [9-13]. En nuestro paciente, la puerta de entrada fue un pinchazo accidental con un clavo probablemente contaminado con la micobacteria. Además, el crecimiento de una micobacteria no tuberculosa como este caso suele suponer el cambio del tratamiento inicialmente prescrito, junto con una prolongación del mismo en el tiempo.

M. smegmatis produce raramente infecciones en huma-

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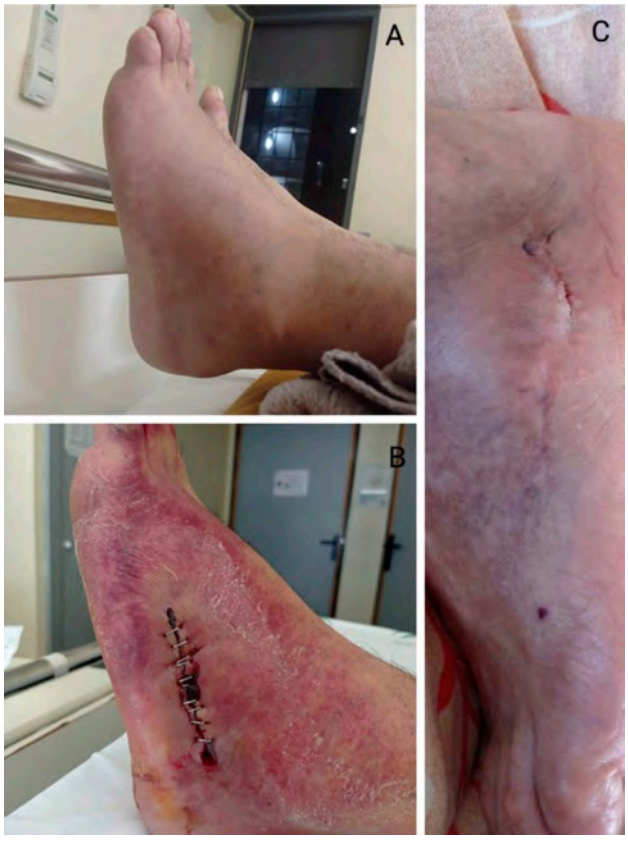

Figura 1 **A: Edema en región lateral externa con inflamación de partes blandas circundantes. B: Pie tras la intervención para desbridamiento quirúrgico. C: Estado del pie un año después del ingreso hospitalario.**

nos, siendo las más importantes las que afectan a piel, tejidos blandos y hueso. Además, suelen requerir intervención quirúrgica y tratamientos combinados y prolongados para su resolución.

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CONFLICTOS DE INTERÉS

Los autores declaran no presentar conflictos de interés

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Erratum

Candel FJ, González Del Castillo J, Julián Jiménez A, Matesanz M.

Ceftolozane-tazobactam in nosocomial pneumonia.

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The authors regret that in the abstract of the manuscript the following is written:

"Ceftolozane is a potent antimicrobial against *Pseudomonas aerugi*nosa, including carbapenem-resistant and multidrug-resistant strains, and is also active against Enterobacteriaceae. It MIC (minimal inhibitory concentration) and MPC (mutant preventive concentration) are close together, allowing to avoid the mutant selection window specifically in the treatment of Pseudomonas aeruginosa infection. The molecule is time-dependent and stable when reconstituted at room temperature, facilitating safe and effective dosage optimization in frail and critically ill patients. It has been shown to be non-inferior to meropenem in the treatment of nosocomial infection in the ASPECT-NP study **but superior in post-hoc studies in the subgroup of patients with ventilator-associated pneumonia**, without the emergence of resistance during treatment. It is FDA approved at a dose of 3 g every 8 hours in the treatment of nosocomial pneumonia (HABP/VABP) in adults."

This should read instead:

"Ceftolozane is a potent antimicrobial against *Pseudomonas aeruginosa*, including carbapenem-resistant and multidrug-resistant strains, and is also active against Enterobacteriaceae. It's MIC. (minimal inhibitory concentration) and MPC (mutant prevention concentration) are close together, allowing to avoid the mutant selection window specifically in the treatment of Pseudomonas aeruginosa infection. The molecule is time-dependent and stable when reconstituted at room temperature, facilitating safety and effectiveness. dosage optimization in frail and critically ill patients. It has been shown to be non-inferior to meropenem in the treatment of nosocomial infection in the ASPECT-NP study **but superior in post-hoc studies on the subgroup of patients with ventilated hospital acquired bacterial pneumonia (vHABP)**, without the emergence of resistance during treatment. It is FDA approved at a dose of 3 g every 8 hours in the treatment of nosocomial pneumonia (HABP/VABP) in adults.

The authors would like to apologise for any inconvenience caused.