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Review

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Air pollution and health prevention: A document of reflection

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ABSTRACT

Ambient air quality, pollution and its implication on health is a topic of enormous importance that is normally dealt with by major specialists in their particular areas of interest. In general, it is not discussed from multidisciplinary approaches or with a language that can reach everyone. For this reason, the Health Sciences Foundation, from its prevention area, has formulated a series of questions to people with very varied competences in the area of ambient air quality in order to obtain a global panorama of the problem and its elements of measurement and control. The answers have been produced by specialists in each subject and have been subjected to a general discussion that has allowed conclusions to be reached on each point. The subject was divided into three main blocks: external ambient air, internal ambient air, mainly in the workplace, and hospital ambient air and the consequences of its poor control. Along with the definitions of each area and the indicators of good and bad quality, some necessary solutions have been pointed out. We have tried to know the current legislation on this problem and the competences of the different administrations on it. Despite its enormous importance, ambient air quality and health is not usually a topic of frequent presence in the general media and we have asked about the causes of this. Finally, the paper addresses a series of reflections from the perspective of ethics and very particularly in the light of the events that the present pandemic raises. This work aims to provide objective data and opinions that will enable non-specialists in the field to gain a better understanding of this worrying reality.

Keywords: Ambient air, quality, public health, nosocomial infection, invasive aspergillosis, measurement systems, respiratory infections.

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Calidad del aire ambiente y prevención de la salud: Un documento de reflexión

RESUMEN

La calidad del aire ambiente y su implicación en la salud es un tema de enorme importancia que normalmente es tratado por grandes especialistas en sus particulares áreas de interés. En general, no es discutido desde enfoques multidisciplinares ni con un lenguaje que pueda llegar a todos. Por ese motivo, la Fundación de Ciencias de la Salud desde su área de prevención, ha formulado una serie de preguntas a personas con competencias muy variadas en el área de la calidad del aire ambiente para obtener un panorama global del problema y de sus elementos de medida y control. Las respuestas han sido producidas por especialistas en cada tema y han sido sometidas a una discusión general que ha permitido alcanzar conclusiones en cada punto. El tema ha sido dividido en tres grandes bloques: el aire ambiente externo, el aire ambiente interno, principalmente en el medio laboral, y el aire ambiente hospitalario y las consecuencias de su mal control. Junto con las definiciones de cada área y los indicadores de buena y mala calidad, se ha apuntado a algunas necesarias soluciones. Hemos tratado de conocer la legislación vigente sobre este problema y las competencias de las distintas administraciones sobre el mismo. Pese a su enorme importancia, la calidad del aire ambiente y la salud no suele ser un tema de frecuente presencia en los medios de comunicación generales y hemos preguntado sobre las causas de ello. Finalmente, el documento aborda una serie de reflexiones desde la perspectiva de la ética y muy particularmente a la luz de los acontecimientos que la presente pandemia plantea. Este trabajo pretende aportar datos objetivos y opinión que permitan a los no especialistas en el tema conocer mejor esta preocupante realidad.

Palabras clave: Aire ambiente, calidad, salud pública, infección nosocomial, aspergilosis invasora, sistemas de medición, infecciones respiratorias

INTRODUCTION

Air quality is a subject of unquestionable interest for the population, for health authorities, for scientists and technicians involved in one way or another and, consequently, for the political world. However, its complexity, its multiple technical aspects and the different approaches to this subject from different fields mean that an overall view is often lacking. The quality of external ambient air does not necessarily follow the same parameters as in the working environment, and hospital air problems have specific consequences that are not always understood from outside the healthcare world.

Very often, experts in one of these aspects ignore the quality parameters and the consequences of their lack of control in areas other than their own.

For this reason, the Health Sciences Foundation, from its area of prevention, has motivated a multidisciplinary meeting so that different experts in some of the many facets of air quality control, could answer questions, apparently elementary, but not always known by all, that would help to better understand this issue and its very serious implications for the health of all.

The different authors responded in writing to the questions posed to them, shared the information with the rest of the participants and conclusions were reached after the discussion of each topic.

The following document is the result of these activities and we have divided it into 3 thematic areas: ambient air in the community, ambient air in the workplace and ambient air in the hospital environment.

FIRST BLOCK: AMBIENT AIR IN THE COMMUNITY

WHAT IS THE RELATIONSHIP BETWEEN OUTDOOR AIR POLLUTION, DISEASE AND MORTALITY?

Bernardino Alcázar Navarrete

Environmental pollution is a global threat that has high impacts on human health and ecosystems, with emissions and concentrations that have been progressively increasing in recent years around the world. Air pollution is currently considered the most important environmental risk factor for human health and is a leading cause of premature death and disease [1-3]. In Europe, air quality remains below the level considered optimal in many areas despite efforts to reduce emissions and air pollutants [4].

The effects of air pollution on human health include primarily premature deaths from cardiovascular disease, including ischemic heart disease and cerebrovascular disease, followed by deaths due to respiratory disease and lung cancer. In addition, both short- and long-term exposure to air pollution can lead to reduced lung function, increased individual susceptibility to respiratory infections, and aggravation of bronchial asthma. On the other hand, exposure to environmental pollutants is associated with negative impacts on fertility, pregnancy, newborns, and children.

Different studies have shown a consistent association between levels of environmental pollution and all-cause mortality and also specific mortality due to cardiovascular or respiratory disease, both in the short and in the medium and long term. In an international study involving more than 600 cities around the world, exposure to 10 μg increases in mean suspended particulate matter (PM) concentrations [5] was associated in the short term with an increase in overall, cardiovascular and respiratory mortality. Similarly, increases of the same magnitude in mean daily PM were also associated with increases in overall, cardiovascular and respiratory mortality.

Air pollution is also associated with increases in long-term mortality in the European population. Within the ESCAPE (European Cohort Study for the Effects of Environmental Pollution) initiative, this effect was analyzed using data from

22 European cohorts, with an average follow-up of 13.9 years, showing an effect of PM on mortality (7% increased risk of death per 5 μg/mm^3). These effects were also observable if data were selected from participants with exposure levels below the thresholds recommended by the authorities [4].

In Spain, the most recent available data indicate that 15.3% of the Spanish urban population is exposed to levels of ozone (O_3) above the EU recommended standard, 3.6% of the population is exposed to levels of nitrogen dioxide (NO_2) above the recommended standard and 0.1% is exposed to excessive levels of PM. It is true that exposure to these environmental pollutants has undergone a progressive decrease in the last decade thanks to the efforts of different governments, but there is still work to be done.

According to the data consulted for 2018, estimates tell us that in Spain there were 23,000 premature deaths due to exposure to PM, 6,800 premature deaths attributable to NO_2 and 1,800 deaths attributable to O_3, which would give us a total of 31,600 premature deaths attributable to environmental pollution in a year.

In addition to these data, environmental pollution, as previously mentioned, is responsible for the loss of years of life derived from its effects both in the short and long term. It was estimated for 2018 a loss of more than 350,000 years of life in the Spanish population attributable to environmental pollution, derived from 254,700 years of life lost due to PM, 75,400 years of life lost due to NO_2 and 20,600 years of life lost due to O_3. In population-adjusted terms, these losses would be 573, 170 and 46 years of life/100,000 inhabitants for PM, NO_2 and O_3, respectively.

CONCLUSION:

The impact of environmental pollution on the health of the population is indisputable, both in the short and long term, with increases in mortality due mainly to cardiovascular and respiratory causes, in addition to other health effects that can have repercussions on the quality and duration of life.

HOW DO WE DEFINE WHAT IS AN OUTDOOR AIR OF GOOD QUALITY? WHAT ARE THE CRITICAL PARAMETERS IN OUTDOOR AMBIENT AIR QUALITY CONTROL? WHAT MEASURES SHOULD BE TAKEN TO IMPROVE OUTDOOR AIR QUALITY?

Xavier Querol Carceller

An air pollutant is any substance present in the air that may have harmful effects on human health, the environment or property of any nature. The increase in the concentration of atmospheric pollutants in outdoor ambient air (street, parks, industrial, rural, and remote areas) causes deterioration of air quality. This deterioration occurs at different scales. Thus, in cities, emissions of urban, industrial, and domestic pollutants have an impact on air quality in the same area where they are emitted. On the other hand, cities and rural and remote areas can see their ambient air deteriorated by the transport of pollutants produced tens, hundreds or even thousands of kilometers away. Examples include tropospheric ozone, acid rain or incursions of Saharan dust masses. The critical WHO normative target pollutants are particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), tropospheric ozone (O_3) and Benzo(a) pyrene (BaP). Any pollutant that has a WHO normative reference value should be kept below the reference values.

The latest study on "The global burden of disease", published in The Lancet, concludes that exposure to polluted air is the fourth leading risk factor for mortality on a global scale, behind high blood pressure, smoking and inadequate diet. This impact also has another associated economic effect, estimated by the World Bank at 4% of global GDP [5,6].

The European Environment Agency [7] quantifies the annual premature deaths in the European Union due to exposure to PM2.5 at 374,000, and recalls that in 1990 this impact reached one million. The same Agency states that 74% of the European population breathed outdoor air that exceeded the WHO guideline value for this pollutant. The maximum levels of NO_2 are not complied with in some of our cities and the Agency estimates that 54,000 premature deaths per year are attributable to its impact on health. With regard to O_3 levels, 70% of the Spanish territory does not comply with the normative target values for human health and 99% of the population of the Europe of -28 breathes outdoor air with concentrations above the WHO guideline level. Finally, BaP is highly carcinogenic, and its levels have increased with the use of agricultural, domestic and residential biomass burning.

In a typical Spanish city, road traffic contributes 70% of the NO_2 breathed by its citizens. And within the traffic about 90% of this contribution is due to diesel vehicles, especially those prior to 2019. In the case of $PM_{2.5}$, road traffic is also responsible for 30% of the $PM_{2.5}$ and PM_{10} we breathe, and not only because of exhaust pipes, but also because of brake and wheel wear. Industry can still contribute 20% of PM, construction sites 10%, ports 5%, ... In the case of BaP, the highest levels recorded in Spain are from rural areas with high domestic-residential and/or agricultural biomass burning. Finally, O_3 is the most complex pollutant. It is secondary (not emitted by emission sources but formed in the atmosphere from reactions between NO_2 and volatile organic compounds), so to reduce its levels it is necessary to act on its precursors, although knowing how to do this is still scientifically and politically complex. In addition, there are unregulated pollutants, such as ultra-fine particles (those smaller than 0.1 microns) and black carbon (the product of the imperfect combustion of fossil fuels or biomass), which have a high impact on health and, in the opinion of a large part of science, deserve to be regulated. In both cases their main source in urban areas is road traffic.

To improve air quality, the most environmentally advanced cities (Scandinavian, Swiss, Canadian, Australian) have for years implemented measures that have enabled them to record the lowest pollution levels in the urban world, but also in rural areas, where air quality problems can also occur. It is

important to note that air quality is a characteristic of a society, and that the most cultured and advanced societies have the best conditions in this regard.

In the case of NO_2, measures have focused on reducing the number of metropolitan vehicles circulating by means of [8]

1) well-developed, fast, economical and comfortable metropolitan and urban public transport;

2) reduction of the number of urban vehicles circulating through urban tolls and restriction of outdoor parking to residents only;

3) low emission zones that do not allow the circulation of the most polluting older vehicles and favor the most eco-efficient ones;

4) efficient logistics of urban distribution of goods and cabs (reducing the number of trips through intelligent logistics, night-time deliveries, hybridization and electrification of vehicles, ...); and

5) urban redesign to gain space for the vehicle in favor of green and pedestrian areas, and to separate traffic from hospitals, schools, primary care centers, geriatric centers, playgrounds, etc.)

For $PM_{2.5}$ these measures may be partially effective, but measures have also been taken on industrial emissions, ports, airports, construction-demolition and domestic and residential emissions. Thus, for both $PM_{2.5}$ and BaP, low emission certification for biomass boilers and the use of certified biomass (natural origin, low humidity and ash) is mandatory [9].

For O_3 the situation is more complex [10, 11], measures should be taken not only at the urban level but also at the regional, national and European levels, in terms of reducing emissions of precursors (NO_2 from traffic, industry and electricity generation mainly) and volatile organic compounds (traffic and industry mainly, but also from the use of cleaning products, paints, resins, ...).

CONCLUSION:

The critical pollutants are suspended particulate matter (PM_{10}, and $PM_{2.5}$), nitrogen dioxide (NO_2), tropospheric ozone (O_3) and Benzo(a)pyrene (BaP).

Control measures have focused on reducing the number of metropolitan vehicles circulating, but measures have also been taken on industrial emissions, ports, airports, construction-demolition and domestic and residential emissions.

HOW DOES AIR POLLUTION AFFECT MORE THAN JUST CARDIOVASCULAR AND RESPIRATORY DISEASES? IS THERE A RELATIONSHIP BETWEEN COVID-19 AND AIR POLLUTION? WHY IS NOISE POLLUTION NOT CONSIDERED AS PART OF AIR POLLUTION?

Cristina Linares Gil

According to the World Health Organization (WHO), 90% of the world's population currently lives in areas where environmental pollution levels acceptable for health protection are exceeded [12]. Historically, air pollution has been linked to respiratory and cardiovascular health problems, but every day more and more studies are published on the impact on other organs. In 2013, the IARC (International Agency for Research on Cancer) classified air pollution as a major carcinogen [13] and in 2018 a review study was already published with data from different cohorts in Europe linking air pollution to breast cancer [14], especially with NO_2. Other studies [15] have also pointed out that there is an association between $PM_{2.5}$ concentrations and mortality from cancer of any origin and especially in the upper digestive tract. Pollution is also related to endocrine diseases such as diabetes. The study by Alderete et al. [16] summarizes the scientific evidence that air pollution is a new risk factor for various metabolic dysfunctions and type 2 diabetes.

At the behavioral level, air pollution is also related to the risk of anxiety and depression. A study conducted in Barcelona, between 2013-2014, shows increased cases of depression and use of medications such as benzodiazepines and antidepressants as the levels of exposure to air pollutants increase [17]. Air pollution has also been linked to cognitive ability in adults. A review of studies linking air pollution and Parkinson's disease establishes that exposure to NO_2, CO and O_3 may increase the risk of Parkinson's disease [18] and a study carried out in Madrid shows that hospital admissions for Alzheimer's disease increase in relation to $PM_{2.5}$ concentrations [19].

Of particular importance is the impact of air pollution on children's health. There is growing evidence that exposure to air pollutants during periods of fetal life and infancy can have very long-term effects. Health impacts occur even at lower pollutant concentrations than in adults [20] because of the vulnerability of the accelerated cellular growth that occurs at this stage for the formation of the nervous, reproductive and endocrine systems [21] among others; as well as the fact that the physiological pathways are metabolically more immature and the mechanisms of elimination of exogenous compounds from the organism are also less developed and less effective. Exposure of children to O_3 and PM is associated with an increased likelihood of bronchitis and other respiratory diseases in the postnatal stage, while intrauterine exposure to nitrogen dioxide and particulate matter has significant negative effects on fetal growth and anthropometric parameters at birth [22,23]. On the other hand, COVID-19 and the mobility limitations established to try to contain its spread during the period of confinement in Spain, have led to a decrease in pollutant emissions. This reduction has been of more than 50% in NO_2 emissions and almost 20% in PM_{10} emission [24]. As to whether air pollution may be a risk factor in the transmission of the SARS-CoV-2 virus, two hypotheses are currently being considered, both of which are complementary:

a) It is being investigated whether the polluting particles themselves are capable of viably transporting the new virus, as has been demonstrated in previous studies with other ty-

pes of biological material: bacteria, viruses, fungi and pollen grains [25]. The explanation for this mechanism can be found in recent research according to which particulate matter may act as a vector for the spread of the disease [26-28]; places with higher concentrations of PM_{10} would be associated with regions with a higher number of COVID-19 cases. This same study, but more extended, has found traces of SARS-CoV-2 RNA in PM samples measured in both industrial and urban environments. The hypothesis is based on the fact that aerosol particles containing the virus of between 0.1 and 1µm can travel farther when bound to pollutant particles of up to 10µm as the resulting particle is larger and less dense than a respiratory droplet, so it could increase its residence time in the atmosphere.

b) The second hypothesis focuses on the increased cardiorespiratory vulnerability of people who are regularly exposed to high levels of pollution in cities. According to the WHO, 1 in 7 patients with COVID-19 suffer respiratory difficulties and other serious complications [29] and to date, factors associated with COVID-19 mortality include: advanced age (higher risk in >65 years) and the presence of comorbidities, including hypertension, diabetes, cardiovascular and cerebrovascular disease. Also documented in relation to this new disease are: vascular inflammation, myocarditis and cardiac arrhythmias.

Finally, it is important to note that air pollution includes both traditional chemical air pollution and pollen pollution as well as thermal, light, electromagnetic and, of course, noise pollution. Although when air pollution is almost always referred to as chemical pollution, in an urban environment and from the point of view of its impact on health, chemical pollution is just as important as noise pollution [30].

CONCLUSION:

Environmental pollution is a major carcinogen, is a risk factor for various metabolic dysfunctions such as type 2 diabetes, increases the risk of anxiety and depression, and influences fetal and neonatal health.

It was initially hypothesized that particulate matter could act as a viable transport vector for SARS-CoV-2, although recent research does not appear to support this hypothesis. It is important to note that air pollution includes both traditional chemical and pollen pollution as well as thermal, light, electromagnetic and noise pollution.

HOW IS THE DETECTOR NETWORK IN SPAIN? ARE THERE DIFFERENCES BY AUTONOMOUS COMMUNITIES? IS IT SUFFICIENT?

Miguel Angel Gil Amigot

The Network of Environmental Pollutant Detectors in Spain is based on a system of monitoring stations equipped with sensors and automatic analyzers distributed in representative locations by zones affected by air quality. This zoning serves to group areas with similar characteristics or homogeneous behavior in relation to air quality and environmental pollutant thresholds [31].

The determination of the different zones and the location of each control and monitoring station is the responsibility of the Autonomous Communities (CCAA). In addition to the network controlled by the Autonomous Communities, there are two other types of monitoring networks. On the one hand, the state network managed by the Spanish Meteorological Agency (AEMET), which is responsible for measuring air quality in remote rural environments and aims to obtain information on transboundary and background pollution in order to comply with current regulations [32]. On the other hand, the network of detectors controlled by local entities or municipalities is developed in order to monitor the main pollutants in certain locations.

In addition to the air quality homogeneity criteria, the air quality legislation, Royal Decree 102/2011 on air quality improvement, requires the Autonomous Regions to justify the division of the zones considering a certain population density and a common ecosystem in each one of them. As an example, the Autonomous Community of Aragon follows a methodology for zoning its territory [33]. On the one hand, the historical air quality data from the detector stations is studied, comparing the data from different stations, the meteorological factors of each area and the topography of the territory. Once the data for the territory has been obtained, measures are taken to ensure that the characteristics in terms of air quality and geography are the same in each area and to delimit as far as possible the areas where there is a high level of concentration (since the restrictions required by law are greater).

All the monitoring stations of the regional and local network in Spain measure the concentrations of gaseous pollutants (NO_2, O_3, CO...) and particulate matter ($PM_{2.5}$, PM_{10}) in the air that are harmful to health and the environment. It is a monitoring network with more than 600 fixed measurement stations in which a wide variety of pollutants are recorded and controlled to estimate the risks and associate the effects on health resulting from exposure to various pollutants in each area of the Spanish territory [34-36].

Stations can be classified by type of area and by type of main pollutant influencing the site. In relation to the type of area, the station can be urban, if it is placed in areas that are continuously built-up; suburban, if it is in places where there is no continuous building and there are separations from lakes, forests, parks...; or rural, when it does not meet any of the previous criteria. On the other hand, in relation to the type of pollutant influencing the zone, it can be classified as a traffic station, if the main pollutant in the zone is vehicle emissions; industrial, when the emission comes from industry; or background, when no predominant emission is detected.

The reason why each zone is evaluated by means of a number of stations and a type of station determined by each Autonomous Community is justified by the impossibility of measuring air quality at all points of the territory. In line with this reasoning, it is true that the location of the monitoring and control stations in each area of Spain can be a determining factor

in the measurement of the levels of certain pollutants. That is to say, it is not the same to place a traffic station very close to one of the busiest and most congested roads in a large city where it is obvious that very high concentrations of pollutants will be registered (for example, NO_2 emissions from vehicles will be directly registered in these stations), than to build the station in a place further away from traffic and high congestion in that same city. Since there is no specific standard related to the exact location of station placement, it is very difficult to reflect the reality of variations in pollutant exposure levels.

Finally, it should be noted that although each Autonomous Community divides its territory into air quality assessment zones, in the end, Spanish legislation requires a series of criteria for the division of the zones. It is true that in the most populated and busiest cities in Spain, where the highest levels of pollution are detected, i.e. Madrid, Barcelona and Valencia, a greater number of control stations are concentrated and more rigorous action plans and protocols are developed to obtain the values allowed by law.

CONCLUSION:

The air quality monitoring network in the national territory is correctly distributed in cities and towns and it is sufficiently sophisticated for the detection of environmental pollutants. They send, in real-time, the results recorded for the preparation of evaluation reports and implementation of plans for the reduction of pollutants in the environment, although it is true, that there is room for improvement at least as far as unification of criteria is concerned.

WHAT DISEASES ARE DIRECTLY RELATED TO AIR POLLUTION?

Isabel Urrutia

Recent work indicates that the health impact attributable to air pollution is substantially higher than previously assumed, and estimates excess mortality attributed to air pollution at 790,000 deaths per year in Europe alone (Figure 1). Although air pollutants can damage virtually every organ in the human body, it is cardiovascular and respiratory diseases that cause the most deaths. It is estimated that around 500,000 lung cancer deaths and 1.6 million COPD deaths worldwide can be attributed to air pollution. In Spain, it is estimated that there are more than 5,000 deaths per year from ischemic heart disease, more than 2,000 from strokes, almost 3,000 from COPD, 1,216 from pulmonary neoplasms and more than 1,000 from lower respiratory tract infections that would not occur if we did not breathe polluted air.

COPD is characterized by persistent airflow limitation associated with chronic inflammation of the airways and lungs in response to exposure to particles and gases. Active smoking remains the main risk factor, but other factors are increasingly well known, such as occupational exposures, infections and

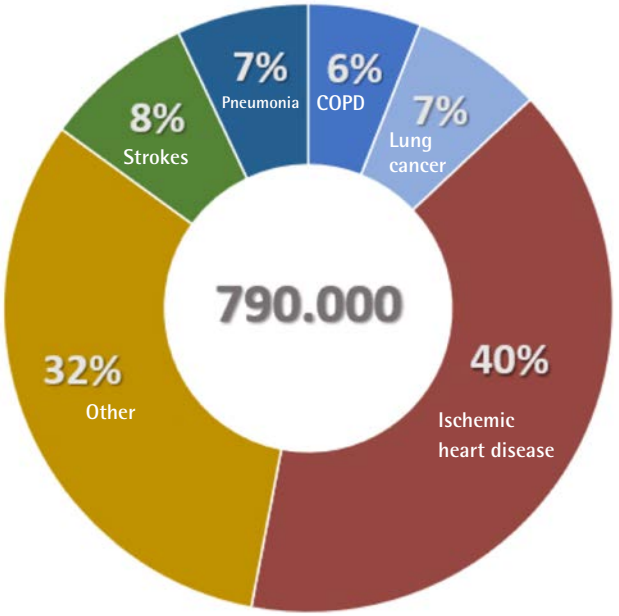

Figure 1 | **Deaths per year in Europe due to air pollution**

the role of air pollution. COPD is the fourth leading cause of death both in Spain and worldwide, and it is estimated that in the coming years it will climb one more place in this fateful ranking [37]. Worldwide prevalence is estimated at 11.7% with very high underdiagnosis rates that may exceed 70%.

COPD patients are more vulnerable to the effects of air pollution. The main mechanisms underlying the adverse health effects of environmental exposure to pollutants are related to oxidative stress and inflammation. Apart from the fact that particulate matter can move into the bloodstream and create vascular dysfunction with potential systemic effects that decompensate the frequent cardiovascular comorbidities of these patients, oxidative stress related to air pollutants can directly damage the airway epithelium and alter the immune response. At present, there is sufficient scientific evidence to consider environmental pollution as a direct cause of COPD. This is reflected in the favorable positioning of the main clinical practice guidelines for the management of COPD, both national and international [38-40] . Ambient concentrations of particulate matter (PM) and nitrogen dioxide (NO_2) have been associated with an increased prevalence of COPD. For example, a higher year-round average $PM_{2.5}$ concentration has been associated with an increased prevalence of COPD with an adjusted odds ratio (OR) of 2.4 for concentrations between 35 and 75 $\mu g/m^3$ and 2.5 for concentrations above 75 $\mu g/m^3$, respectively, compared with the lower limit of 35 $\mu g/m^3$. However, this etiological role is even more evident if we consider indoor air pollution. We spend about 90% of our time indoors, so the atmosphere in these spaces is very important for our health. Some 3 billion people cook and heat their homes with open fires and stoves burning biomass (wood,

animal dung or agricultural waste) and charcoal. This practice occurs mainly in developing countries. Each year, more than 4 million people die prematurely from diseases attributable to household air pollution and COPD accounts for 20% of these deaths. Thus, environmental pollutants become the main cause of COPD in some regions of the world among certain population groups, such as women with limited economic resources in some areas of Southeast Asia.

Environmental pollution has also been recognized as a precipitating factor in COPD exacerbations, which accelerate the deterioration of respiratory function, contribute to increased mortality and significantly increase healthcare costs. In the case of the COVID pandemic, we know that SARS-CoV-2 is spread through the air by so-called Flugge droplets. Particles smaller than 5µ can remain in the air even for hours and spread far away. Some authors have described that PM can both increase transmission distance and infectivity in the aerosol with a "booster" effect.

The impact that air pollution has on the extent and prognosis of COVID-19 remains to be elucidated. In a recent study conducted in China between January and February 2020 they observed a positive association between two-week $PM_{2.5}$, PM_{10}, NO_2 and O_3 levels and confirmed new cases of COVID-19. The authors observed that each 10g/m^3 (lag 0-14 days) increase in these pollutants was associated with an increase in new confirmed cases of 2.24%, 1.76%, 6.94%, and 4.76%, respectively.

Italy was another of the major victims of the beginning of this pandemic in Europe. Several Italian authors have stressed that the high spread of COVID in some areas of Northern Italy could be linked to environmental conditions. In addition, the suspended particles, composed of solid and liquid particles, allow the virus to float in the air for longer and over longer distances. In fact, the spread of SARS-CoV-2 infection is found to increase in areas with higher relative humidity while it decreases in warmer climates.

CONCLUSION:

Ambient air pollution is estimated to cause 790,000 deaths per year in Europe. In addition to cardiovascular diseases, the relationship between environmental pollution and Chronic Obstructive Pulmonary Disease is essential. There is also speculation about the relationship between environmental pollutants and a better vehiculation of SARS-CoV-2 particles over longer distances.

SECOND BLOCK: INDOOR AMBIENT AIR QUALITY IN THE WORKING ENVIRONMENT

HOW DO WE DEFINE INDOOR ENVIRONMENTAL QUALITY? WHAT IS THE EFFECT OF AEROSOLS ON SARS-CoV-2 TRANSMISSION? WHAT MEASURES ARE MOST EFFECTIVE IN REDUCING AEROSOLS?

Francisco Vargas Marcos

Indoor Environmental Quality (IQ) is defined in the Une 171330:2008 Standard [41] as "Indoor environmental conditions, appropriate to the user and the activity, defined by the levels of chemical and microbiological contamination and by the values of physical factors". Without good IAC, the risk of numerous diseases such as COVID-19 increases. We spend between 80-90% of our time in indoor environments for work, home, education, sports or leisure. During the COVID-19 pandemic this percentage has risen and has highlighted the importance of living in healthier and safer enclosed spaces that prevent airborne transmission of SAR-CoV-2. Humans generate aerosols or bioaerosols that have been defined elsewhere [42]. It can be stated that SARS-CoV-2 is viable as an aerogenic pathogen continuously emitted with respiration. Its quantity increases when we suffer from respiratory diseases and when we force our voice when speaking, singing or shouting. For these reasons, the transmission of respiratory diseases inside poorly ventilated enclosed spaces can be up to 20 times higher than outdoor transmission. Since the beginning of the pandemic, numerous studies have been published that have observed an increase in the number of outbreaks of COVID-19 caused by aerosols carrying the virus in restaurants, gyms, boats, buses, choirs and other enclosed places with poor ventilation. Several experimental tests on fluid dynamics, aerosol physico-chemistry, permanence, SARS-CoV-2 viability, infective capacity (16 hours), have alerted to the importance of aerosol transmission and the need to apply prevention and control measures in closed, poorly ventilated and crowded spaces [43-46].

This evidence challenged the classical routes of transmission of respiratory diseases accepted by WHO and the scientific community. New knowledge on respiratory emission dynamics indicates that respiratory droplets can reach, under specific conditions, 7-8 meters. Their acceptance has important implications for improving respiratory protection mask design, social distancing recommendations, prevention strategies in air conditioning installations and other public health recommendations.

But to prevent airborne SARS-CoV-2 transmission, the first step was for health authorities, agencies and organizations to accept the published evidence on the role of aerosols in COVID-19 transmission, overcoming political fears of public reaction, the media, opinion polls and social networks. It is clear that there has been a delay in recognizing the impact of air on COVID-19 transmission and in making decisions on the most effective measures for implementation.

Legitimate and justified calls have been published to evaluate how the pandemic has been managed, to learn from mistakes, to provide the necessary resources for research, to improve epidemiological surveillance systems and public health services. However, it should be noted that it is common for too much time to elapse between the publication of solid evidence, its majority acceptance by the scientific community and finally its application by the competent authorities in Public Health or health professionals with respect to a preventive measure, drug, medical or surgical technique.

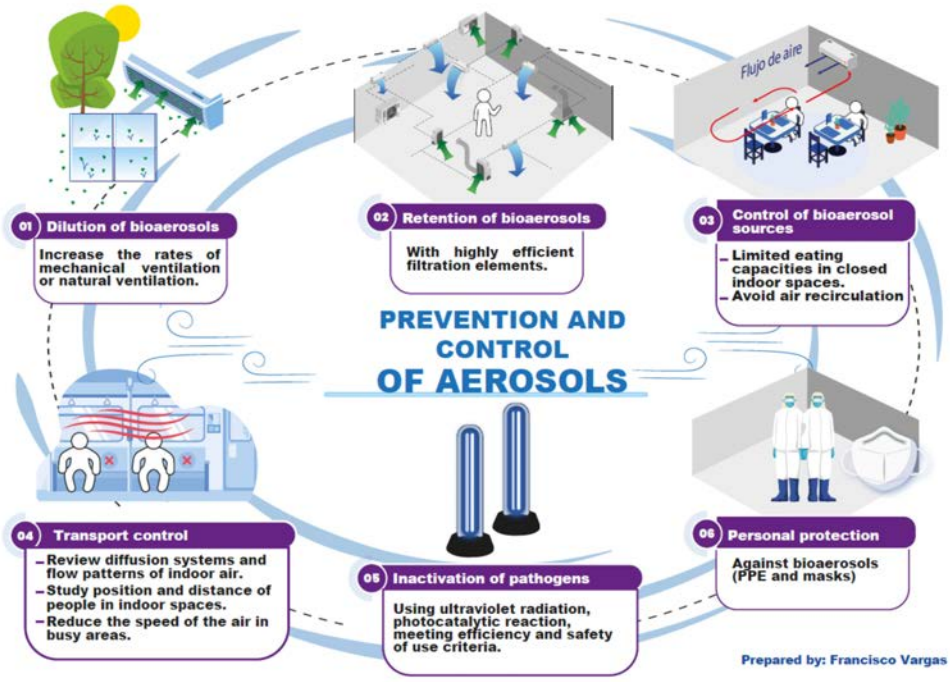

Figure 2 | **Prevention and control of pathogen transmission by aerosols.**

One of the first articles published in our country calling for airway prevention measures was a review of scientific evidence on the transmission of SARS-CoV-2 by respiratory droplets, contaminated objects and aerosols [47]. This document served as the basis for the Ministry of Health to promote the drafting of a technical document containing the Recommendations for the operation and maintenance of air conditioning and ventilation systems to prevent the spread of SARS-CoV-2 [48].

The ECDC [49], WHO [50] and American CDC [51] have accepted the evidence of SARS-CoV-2 transmission via aerosols, proposed measures to reduce the risk of exposure to aerosols and described the role played by heating, ventilation and air conditioning systems. In the light of the new evidence, they admit the possibility that in certain indoor environments with many people who do not keep a safe distance, without facial protection, in closed and poorly ventilated spaces, airborne transmission combined with droplet (large) and contact transmission may occur.

Subsequently, the Spanish Ministry of Health published a technical document supported by experts and several SSCCs specialized in aerosols that recognizes the importance of airborne transmission and proposes prevention measures [52].

Summary of recommendations for the prevention of SARS-CoV-2 transmission by aerosols.

Preventive measures to avoid SARS-CoV-2 virus transmission should follow a combined strategy of protective measures, so that the combined use of more than one measure achieves better protection. No single protective measure is 100% effective on its own in preventing transmission. At present, the scientific evidence on the effectiveness of each measure in relation to SARS-CoV-2 is still limited and must be weighed against the risks and feasibility associated with its implementation. Figure 2 summarizes the measures for the prevention of SARS-CoV-2 transmission.

1. Dilution of bioaerosols.

- Increase ventilation rates with mechanical ventilation equipment or natural ventilation by opening windows.

2. Retention of bioaerosols.

- Use of filtration elements with high filtration efficiency.

3. Control of sources of bioaerosols.

- Reduce occupancy rates and time spent in the premises. Maintain interpersonal distance.
- Avoid recirculation of air in air conditioning equipment.
- Use of face masks in enclosed areas when social distancing measures cannot be applied.

4. Control of bioaerosol transport.

- Control of the air diffusion system and indoor air flow patterns.
- Study the position and distance of people in indoor premises. Avoid air flows coming from another person.

- Reduce air velocity in the occupied area. Avoid air currents between people in the breathing zone.

5. Inactivation of pathogens in bioaerosols.

- Use of germicidal equipment of physical action that can contribute to reinforce the hygiene of the indoor environment. With two conditions for their use:

  1) Scientific evidence of the effectiveness of the system against SARS-CoV-2 virus.

  2) The dose applied and the residues resulting from its application do not pose any risk to people.

6. Personal protection against bioaerosols.

- Use masks with adequate filtration capacity to avoid transmission from/to other persons. Use of PPE in the work environment.

CONCLUSION:

Indoor Environmental Quality (IQ) is defined in the Une 171330:2008 Standard. Since the onset of the COVID-19 pandemic, numerous studies have been published that have noted an increase in the number of COVID-19 outbreaks caused by aerosols in restaurants, gyms, boats, buses, choirs, and other enclosed places with poor ventilation. The Spanish Ministry of Health published a document proposing measures to prevent the transmission of SARS-CoV-2 by aerosols.

WHAT IS THE RELATIONSHIP BETWEEN OUTDOOR AND INDOOR POLLUTION? WHAT ARE, BROADLY SPEAKING, THE MEASURES TO MAINTAIN HEALTHY AIR IN THE WORK ENVIRONMENT? CAN THESE MEASURES BE APPLIED TO COVID-19 PREVENTION?

Teresa Álvarez Bayona

WHO estimates that 3.8 million deaths occur annually from diseases attributable to indoor air pollution often caused by the use of inefficient solid fuels [53]. In countries such as Spain, people spend between 60% and 80% of their time indoors [54] and the effects of polluted indoor air accumulate in the body regardless of where the pollution occurs. CO_2 is a pollutant that serves as an indicator of indoor air quality associated with human activity. Its use requires reference to the outdoor concentration [55] since in reality, outdoor air is neither "clean" nor "fresh".

The technical measures for the control of indoor air will be aimed at controlling the risks related to the environment: reduce the emission of the source, prevent or reduce its spread through the air and, finally, act on people. When the source cannot be eliminated, nor can the emission be reduced, it is necessary to screen the source. It is a measure whose objective is to interpose a physical barrier that reduces the emission of the pollutant into the air [56].

The next group of measures is aimed at acting on the environment. The most effective measure is ventilation, whether natural, mechanical or mixed. The objective is that, indoors, the "polluted" air is renewed at an adequate rate. As the most effective and cheapest ventilation is natural ventilation, preferably cross ventilation, it should be chosen whenever it is feasible and sufficient [57]. Sometimes, the programming and adjustments of the air conditioning systems should be directed to a greater contribution of outside air flow. The use of appropriate filters for the recirculated air fraction and their maintenance are other key aspects [57].

The latest technical measures in the preventive field are aimed at acting directly on the worker. Many of them coincide with the measures aimed at controlling the source, since the workers to be protected must also be considered as possible sources.

Focusing on the throbbing problem of SARS-CoV, this virus identified in 2019 belongs to the *Coronaviridae* family [58] and its transmission route and behavior is similar to that of other viruses of the same family [59]. It is transmitted by nasopharyngeal secretions through droplets of more than 5 microns and by aerosols from human respiration [60]. In other words, if the focus is avoided, the "contamination" is eliminated. The most direct way is to prevent people from coming to the workplace, for example, by teleworking. As this is not always possible, exposure should be reduced, even if the risk is not eliminated, and measures should be taken to distance and minimize contact. In this case, the barrier is the mask, and the better its efficiency and fit, the lower the emission of aerosols into the environment. There are autonomous governments that have made it compulsory to wear the mask at all times in the workplace [61].

Some studies suggesting the viability of SARS-CoV-2 in aerosol form during three hours [58]. This is the reason for recommendations such as ventilating before entering workstations. But not all spaces have windows or elements that ensure proper air renewal. One situation that occurred at the beginning of the pandemic was to consider fans that remove air as a substitute. Their effect is the opposite: instead of providing "clean" air, they recirculate and concentrate pollutants including aerosols. In these cases, it is necessary to resort to mechanical ventilation, which is more expensive and requires specialized expertise. In the case of SARS-CoV-2, distances of 2 meters will be sufficient to avoid droplets, but this is not the case for aerosols. The aerosol has a medium-dependent aerodynamics influenced by temperature, humidity, and air speed. Thus, increasing the relative humidity above 40% affects its aerodynamics in the sense that it favors the precipitation of aerosols and, therefore, hinders their propagation [59].

All these technical measures to control the transmission of the virus through the air do not work unless the behavior of workers is also changed. In medium- and low-risk companies, the main causes of virus transmission have probably been coffee outings, retirement parties or other social events. For employee awareness to be successful, information must be coherent and adjusted to the level of knowledge of the recipient

so that the worker can apply common sense. Unfortunately, these days, this task has been made more difficult due to the contradictory media over-information that has made the general population's opinion on such a specialized and delicate aspect as this one.

CONCLUSION:

WHO estimates that 3.8 million deaths occur annually from diseases attributable to indoor air pollution frequently caused by the use of inefficient solid fuels. Technical measures for indoor air control should be aimed at eliminating or controlling sources of pollutants, decreasing their spread through the air, and increasing and improving ventilation and air renewal, sometimes including the programming and adjustment of air conditioning systems and the use of appropriate filters. SARS-CoV-2 can remain viable in aerosols for three or more hours and therefore distancing and ventilation measures are recommended.

WHAT IS BEING DONE TO REDUCE AIR POLLUTION FROM INDUSTRY, ARE THERE FEASIBLE PLANS, AND CAN RENEWABLE ENERGIES HELP IMPROVE AIR QUALITY?

Paulino Pastor Pérez

When we talk about indoor environmental quality, we often reflect that we spend 90% of our time indoors, to better visualize the magnitude of this exposure, let us consider that for a 55 year old person, this means 50 years in an indoor environment, divided between residential, work and leisure exposure, therefore, it is clear that enclosed spaces are the main source of exposure to air pollution.

Indoor air quality is conditioned by outdoor air quality, since the first measure to improve it is to ventilate with fresh outdoor air, the problem is that this air does not always meet the thermal or purity conditions (absence of pollutants) to produce an effective improvement of indoor air, so it is necessary to condition and treat the air by purification and filtration systems before introducing it into indoor environments.

Improving indoor air quality usually involves an energy cost, and that paradoxically produces pollution outside, especially if we do it through energy from fossil fuels, so it is essential to work on the decarbonization of our buildings in such a way that we end up achieving the necessary indoor air quality and thermal comfort without compromising the quality of outdoor air.

Fortunately, renewable energies, in generation (solar, thermal, biomass, etc.) as well as the improvement in the forms of energy consumption (aerothermal, geothermal, etc.) and the reduction of the energy demand of buildings through improvements in the envelope and others, are allowing us to approach a point of balance between healthiness and comfort indoors and neutrality in terms of emissions to the atmosphere by the building stock.

Nowadays, building owners, mainly office buildings, are starting to devote more and more resources to achieving sustainable buildings (environmental certifications such as LEED or BREEAM), but in recent years the importance of healthy and comfortable buildings (WELL certification) is also being emphasized.

The environmental trend in the tertiary sector is clear; however, other building sectors are not yet in line with this trend. Residential buildings, industrial buildings, logistics centers, hotels, transportation centers and even shopping centers are still far from starting the decarbonization process on a massive scale.

If we compare the real estate sector with other energy-intensive areas such as transport (electric vehicles), we can be sure that it is still far behind. The recent incentive plans by the administration will most probably help technologies to start to be implemented, because currently the technology exists, but the main barrier is the availability of financial resources for the rehabilitation of buildings.

CONCLUSION:

Improving indoor air quality usually involves an energy cost, and that paradoxically produces pollution outside, especially if it is done through energy from fossil fuels.

It is essential to work on decarbonization by progressing towards environmental certifications such as LEED, BREEAM or WELL.

WHAT IS THE CURRENT SITUATION OF LEGIONELLOSIS IN SPAIN? ARE SUFFICIENT MEASURES BEING TAKEN FOR ITS PREVENTION? WHAT DOES THE LEGISLATION ESTABLISH?

María Luisa Pedro-Botet

Legionella spp. is an intracellular aerobic Gram-negative bacillus that causes pneumonia in both community and hospital settings in the form of sporadic cases or outbreaks. The *Legionellaceae* family has more than 60 species and more than 70 serogroups of which *L. pneumophila* sg 1 stands out in both the aquatic reservoir and in human pathology.

The term legionellosis refers to the clinical manifestations caused by this microorganism and includes mostly the pneumonic form and, less frequently, a febrile form without pneumonia or "Pontiac fever". The most commonly accepted mechanism of transmission to humans is the inhalation of aerosols emanating from colonized water, sanitary or from cooling systems (cooling towers and cogeneration) although exceptionally aspiration is described after oropharyngeal colonization in hospitalized patients with dysphagia.

According to data published by the European Centre for Disease Control (ECDC), a total of 30 countries reported 11,343 cases of legionellosis in 2018 to the European Survei-

llance system, representing an incidence of 2.2 cases/100,000 inhabitants, the highest recorded in recent years. Among the countries that have declared the most cases, France, Germany, Italy and Spain stand out. In Spain, the number of cases declared in 2018 was 1,513 and the incidence was 3.3 cases per 100,000 inhabitants. In the Spanish territory, cases and outbreaks are monitored by the autonomous communities and notified through the National Epidemiological Surveillance Network (RENAVE) to the National Epidemiological Center of the ISCIII.

Legionellosis mortality in Europe stood at 8% in 2018 and 32 outbreaks have been reported in that year accounting for between 2 and 11 affected per outbreak and of which only 6 have originated in hospital environment.

Climate change, the aging of the population, the eventual deterioration of buildings and their water distribution systems and a greater awareness and sensitivity of countries towards the diagnosis and reporting of legionellosis cases to the ECDC undoubtedly justify the increase in cases and incidence of this disease in Europe.

Current legislation does not provide for any action on air quality in the case of legionellosis and, on the contrary, on the design, operation and maintenance phase of water systems that are the source of Legionella infection in humans. In the case of health centers, the ventilation system should be closed, as a measure to stop the possible entry through the windows of aerosols generated outside in facilities at risk for legionellosis. If the hospital has central air conditioners, the humidification, heating (for heating) and cooling (for cooling) chambers should be monitored, since a failure in these systems could lead to the passage of aerosols possibly contaminated by Legionella into the distribution air of the hospital rooms [62-67].

CONCLUSION:

Aerosol-borne microorganisms of the genus *Legionella* are a cause of pneumonic and non-pneumonic infections both inside and outside hospitals. Their prevention is focused on avoiding and treating the colonization of water reservoirs from which aerosols that reach the airway of people can be generated.

WHAT ARE THE HEALTH, SOCIAL AND ECONOMIC COSTS OF POLLUTED INDOOR AIR?

Eduardo Olier Arenas

In 2013, the World Bank and the University of Washington's Institute for Health Metrics and Evaluation estimated that indoor air pollution alone led to wealth losses of around $1.5 billion [68].

There are few studies on the socio-economic effects of indoor air pollution in developing countries. France, however, is one of the countries that have understood the importance of this type of pollution and its harmful social and economic effects. Perhaps not much attention has been paid to this problem because the economic effects of pollution constitute "negative externalities": an economic concept that is difficult to account for in many cases. As a prelude to what follows, we will say that an economic externality is one in which the costs of producing or consuming a good or service, or the benefits of doing so, are not reflected in market prices. In other words, these are side effects that occur when an economic activity does not take into account the costs or benefits that it itself produces. And, in this case, pollution, being a negative externality, causes economic consequences that are difficult to estimate, as it is difficult to evaluate the corresponding market prices.

Indoor air pollution is a fact that has been little studied in general, since more emphasis and effort is placed on policies aimed at mitigating the effects of climate change and, in particular, the effects produced by greenhouse gases. So much so that the current 750 billion euro Next Generation EU Program, approved by the European Council on July 21, 2020, has been approved by the European Council on July 21, 2020 [69], The issue of indoor air pollution is a long-standing economic problem that Ronald Coase, winner of the Nobel Prize in Economics, highlighted as early as 1960 when he discussed the harmful effects of certain factories whose emissions were damaging to the health of the population.

The issue of pollution is an old economic problem that Ronald Coase, winner of the Nobel Prize in Economics, brought to light as early as 1960 when he discussed the harmful effects caused by certain factories, whose emissions were damaging the health of the inhabitants of nearby towns and cities [70]. Coase refuted those economists who sought to solve this problem by taxing polluting industries, since the real problem to be solved — Coase — understood — had to focus on avoiding pollution, not on accepting it by applying a tax treatment; since, in reality, it is a problem related to the social cost of the damage produced, which should consider whether the cost of pollution is greater or lesser than the problem caused by it [70]. This issue can be extended to all the problems related to the pillars of the welfare state enjoyed by advanced countries, which is none other than the analysis between economic efficiency and the problem of equity between those who pollute and those who suffer such effects [71].

This is a circumstance that, in general, does not take into account its full dimension, since the problem is usually alleviated with fiscal or financial solutions through the well-known emissions markets created under the Kyoto Agreements [72]. In what follows, without being exhaustive, we will give some ideas on the socioeconomic problem of indoor air pollution which, in Spain, by the way, has not been an issue that has attracted much attention to date.

The main pollutants in indoor spaces come mainly from three sources: (i) chemical pollutants (volatile organic compounds, nitrogen oxides, carbon monoxide, aromatic hydrocarbons, etc.); (ii) bio-pollutants (molds, dust mites, pets, pollen, cockroaches, etc.); (iii) suspended particles and fibers (asbestos,

artificial mineral fibers, inert particles, etc.)[73]. The philosophy behind this criterion, however, focuses on solving the problem by taxing the supposedly polluting companies, i.e., imposing a tax according to the level of the economic externality produced, which requires knowledge of the type of pollutant and its effects on the environment, in addition to determining the polluting agent. Once again, this mechanism tries to solve pollution problems with new taxes, for which fiscal criteria are imposed with ex-ante criteria, instead of carrying out ex-post analyses, which are necessary to know in detail the undesirable effects of pollution, where they come from and what measures should be taken to avoid them.

With regard to the economic impact of indoor air pollutants, at least two aspects must be considered: (i) the opportunity cost, related to the loss of economic activity due to the illness of workers or, in extreme cases, the loss of human lives, and (ii) the direct cost of pollution on the public or private economy, which is related to the marginal cost that governments or companies have to bear because of pollution; that is, the additional costs that they have to assume due to the polluting event. A circumstance also dealt with by Ronald Coase in his day, which gave rise to the so-called Coase Theorem, according to which, in the absence of monetary transactions, as in the case we are dealing with, private and public costs coincide [74]; It is understood that the market alone will not be able to accommodate the two extremes, and it will be up to the regulator, i.e., the corresponding government, to provide an equitable solution to the problem, in order to find the optimum point between efficiency and equity, apart from the simple application of new taxes. Figure 3 shows the equity vs. efficiency scheme [71].

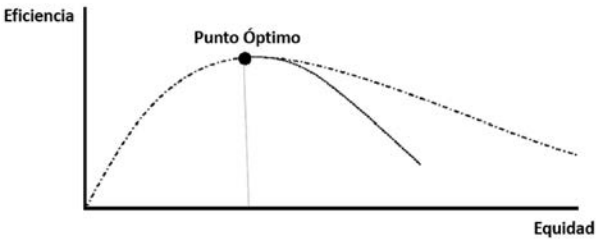

Figure 3 | **Search for tax equity**

One way of expressing the socioeconomic cost produced by indoor air pollution takes the following form for the case of the public costs associated with it:

$$W = \Delta CE + \Delta G \times (1 + \alpha)$$

where: W is the socioeconomic cost; ΔCE the variation of costs due to loss of human lives, degradation of quality of life or production losses; (1 + α) the negative impact on public finances; and ΔG the variation of other concepts such as: retirement or disability pensions, investments in research, added

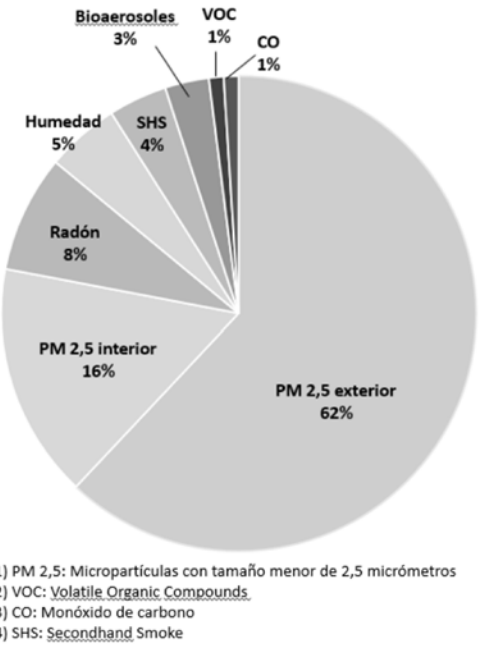

Figure 4 | **Influence of different particles in interior spaces.**

health expenses, etc.; with "x" as multiplication sign [75]. This study, led by Guillaume Boulanger, also shows the health effects of a number of pollutants (benzene, radon, carbon monoxide, tobacco smoke, etc.) in France in 2004: 19,879 deaths, with an impact on morbidity of 26,046 people, and a total cost of 19,443 million euros to the public purse. In addition, a report by the European Parliament [76] reference a study estimating, for 26 European Union countries, a loss of 700,000 years of "healthy life" due to indoor air pollution [77], with a distribution of the produced harm by different particles as it is shown in Figure 4. The risk, as shown here, is greater in the case of microparticles coming from outdoors, so that outdoor pollution is also harmful indoors, with a higher incidence in people suffering from some type of respiratory diseases or dysfunction, both young and old, and, in current times, especially in people suffering from the coronavirus pandemic (COVID-19).

CONCLUSION:

Indoor air pollution is an understudied fact in general, as more emphasis and effort is placed on policies aimed at mitigating the effects of climate change and, in particular, the effects produced by greenhouse gases and outdoor pollution. Indoor air pollution alone leads to wealth losses of around $1.5 billion. In addition to the opportunity cost of lost economic activity due to worker illness or, in extreme cases, loss of human life, there is the direct cost of pollution to the public or private economy, which is related to the marginal cost borne by governments or companies as a result of pollution.

WHAT IS THE RELATIONSHIP BETWEEN AIR POLLUTION AND CLIMATE CHANGE, AND WHAT ARE THE IMPLICATIONS FOR THE HEALTH SECTOR?

Felipe Villar Álvarez

Air pollution and climate change are the two main environmental problems. Both are closely related, but they are not the same. Just as the definition of the former has been well defined above, we can say that climate change, according to the WHO, is a statistically significant variation in the mean state of the climate or its variability, persisting over an extended period of time (usually decades or longer). Climate change is due to natural internal processes or external forcings, and to persistent anthropogenic changes in the composition of the atmosphere. The United Nations Framework Convention on Climate Change defines climate change as "a change of climate that is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and that is in addition to natural climate variability observed over comparable time periods". $PM_{2.5}$ can come from all kinds of combustion, such as from automobiles, factories, wood and agricultural burning, or other activities, and can also affect the climate. Primary pollutants such as soot can absorb heat, thereby increasing local temperatures [78], and secondary aerosols such as sulfate particles cool the climate and contribute to aerosol-cloud interactions [79,80]. Near-surface ozone is another secondary pollutant formed by the interaction of precursor compounds with sunlight, including ultraviolet radiation [81]. The rate of formation depends on temperature. Because of this, ozone increases on hot, cloudless days [82]. On the other hand, wind and dry deposition can reduce their levels [83]. This near-surface ozone formation is the result of chemical reactions that depend on emissions of ozone precursors from natural and anthropogenic sources. The main precursors include several primary and other secondary pollutants such as volatile organic compounds (VOCs), methane (CH_4) and carbon monoxide (CO), which react with the hydroxyl radical (OH) to ultimately produce ground-level ozone. In addition, the formation of hydroxyl radicals is associated with CH_4, another greenhouse gas [84].

Global warming of the planet is accelerated by the emission of greenhouse gases caused by human activities. The main ones are carbon dioxide (CO_2), CH_4 and nitrogen oxide (N_2O). The two main effects of climate change on air quality are the amplification of atmospheric chemistry and the degradation of air removal processes [83]. These will affect primary and secondary pollutants. Rising temperatures, with consequent changes in plant metabolism, will alter emissions of VOCs and secondary organic aerosols, leading to changes in secondary particulate matter levels [85]. Climate change may lead to more forest fires, dust storms and transport of dust particles, which may change the annual average concentrations of $PM_{2.5}$ in $\pm$ 1 $\mu g/m^3$ [81].

Climate change and air pollution can affect each other's health directly or indirectly. Air particles, especially from combustion, and gases such as ozone can increase cardiopulmonary mortality and hospitalizations, and are related to respiratory diseases such as asthma, chronic bronchitis or rhinitism [86,87]. Other diseases associated with air pollution include rheumatic diseases, neurodegenerative diseases, diabetes, premature birth, and cognitive impairment [86,87]. On the other hand, primary and secondary pollutants can drive climate change, which in turn affects public health through, for example, more extreme temperatures [88]. Secondary pollutants such as ozone can also affect crop yields which, in combination with climate change, can affect food safety and public health [89,90].

The direct impacts of climate change, such as the spread of vector-borne diseases, higher temperatures, droughts, severe storms and floods, as well as the mass migration of climate refugees, have consequences for health, through an increase in infectious, cardiovascular, respiratory, mental or allergic diseases, and even the onset of malnutrition. These will disproportionately affect the most vulnerable and marginalized populations, and will increase in intensity over time [91].

Each country's healthcare sector releases greenhouse gases and contributes to carbon emissions through energy consumption, transportation, and the manufacture, use and disposal of products [91]. The climate footprint of the health sector is equivalent to 4.4% of global net emissions (1.6 gigatons of CO_2 equivalent) [92]. Emissions emanating directly from health facilities make up 17% of the sector's global footprint, while indirect emissions from purchased energy sources such as electricity, steam, cooling and heating account for another 12%. The majority of emissions (71%) come from the health sector supply chain [91].

CONCLUSION:

Air pollution and climate change are closely related and share the same main culprit: the burning of fossil fuels. Finding solutions to reduce air pollution and climate change requires joint actions through clean energy to reduce air emissions, reduce mortality and disease occurrence, and reduce health care costs.

THIRD BLOCK: AMBIENT AIR AS A CAUSE OF HOSPITAL AND HEALTH CENTER-ACQUIRED DISEASE

WHAT DO WE MEAN BY HEALTHY AMBIENT AIR IN HOSPITALS AND HEALTHCARE CENTERS?

Ángel Asensio

We could define a healthy air environment in healthcare facilities as one that provides comfortable activity and safe conditions for both patients and workers or visitors [93].

Comfort and safety criteria will often overlap. Comfort will depend on parameters such as temperature, humidity and air velocity and safety will cover aspects from the point of view of protection against harmful biological, physical or chemical agents.

In the healthcare environment, of all the risks associated with ambient air, and leaving aside the risks common to other workplaces, biological risks are the most important. And these risks will be proportional to the vulnerability of the patients. Therefore, the maintenance of good air quality will in many cases be an important non-pharmacological strategy for the prevention of infections and the maintenance of health [94].

Heating, ventilation and air conditioning (HVAC) activities, in addition to their primary purpose of providing a comfortable and safe environment for patients and others, play a fundamental role in preventing patient infection [95,96]. The essential functions of HVAC systems include heating and cooling, humidification and dehumidification, ventilation and air distribution, and filtering to remove dust particles and biological contaminants such as fungi, viruses or bacteria from the air. These air conditioning functions are important for the prevention of contamination and cross-contamination, and for the protection of both patients and workers [97].

Numerous diseases are related to poor air quality management in hospitals. From filamentous fungal infections (*Aspergillus*,...) to the transmission of bacteria (*Enterobacteriaceae*, non-fermentative Gram-negative, Gram-positive, *Legionella*,...), mycobacteria (tuberculosis,...) or viruses (RSV, varicella, influenza, rhinovirus, coronavirus,...).

Patients with severe immunosuppression, those undergoing surgery, and those housed in Intensive Care Units will be very vulnerable groups of patients to airborne biological agents. Therefore, it will be in the rooms where these patients are housed where air safety conditions must be more stringent.

When we need to create a special protective environment for patients at very high risk of infection, we must ensure that the quality of the ambient air is ultra-clean by means of very high efficiency filtration (High Efficiency Particulate Air filter, or HEPA filters) and by ensuring that the pressure inside the room is positive so that when the doors are opened, air currents entering the room from the potentially contaminated outside are prevented.

On the other hand, we must ensure that patients with airborne infections are housed in controlled environments that prevent contagion to other patients or workers. This is the case of infections caused by microorganisms that can generally be sent to the environment from the respiratory tree of infected patients, and which, depending on the type of vehicle (size of the exhaled particles) and the viability and survival of the agents, can contaminate patients or professionals. In these cases, HVAC systems must be adapted to contain and purify the agents, creating conditions of airtightness, negative pressure, purification and exhaustive air renewal.

The most complex situation occurs when we must accommodate in a protective environment patients who in turn can be infectious for others in which case the HVAC systems must ensure through intermediate chambers between the patient's room and the corridors, a positive pressure for the patient and in turn positive between the corridor in front of the intermediate chamber.

Another important section in the environmental safety of healthcare facilities is related to airborne physical or chemical noxious agents such as dusts, gases and irritants that must be addressed by measures including containment or elimination of the emitting source, filtration or purification.

Finally, while the mechanism of transmission of infections by contact is the most frequent, that of airborne transmission is more difficult to control, and one where engineering sciences play an important role in limiting the spread of microorganisms.

CONCLUSION:

We understand healthy hospital air to be that which provides comfortable activity and adequate safety conditions for both patients and workers or visitors. The risks of hospital air for patients will be proportional to their vulnerability.

WHAT TYPES OF AMBIENT AIR PROTECTION LEVELS SHOULD BE IN PLACE IN HOSPITALS AND HEALTHCARE FACILITIES? ARE THERE SPECIAL MEASURES TO PREVENT COVID-19?

Gloria Cruceta Arboles

If there is a building or space where air quality becomes the main protagonist of our health, it is in hospitals and healthcare centers. Immunosuppressed patients are susceptible to airborne infections from microorganisms (bacteria, fungi, viruses...) that may be common in the general environment, but that can cause nosocomial infection in sick persons, with an often irreversible impact.

The protection of the ambient air in hospitals is achieved through three fundamental means, which are:

1-Ventilation.

2-Filtration.

3-Purification.

The combination of these elements must be studied in function of the patient's needs required by the patient, the intervention to be performed, or the complementary actions to be carried out.

Ventilation is very important as it dilutes the contaminants, whether chemical or biological, and there are regulations in this regard, in RD 1027/2007, RITE, which categorizes air quality in healthcare centers as IDA 1, which means maximum ventilation.

Filtration is essential to limit the passage of particles, knowing that microorganisms are always suspended in them, it is basic to restrict their propagation in the air. In hospitals there are controlled environment rooms, which, in order to protect the patient, are equipped with high efficiency HEPA filtration, being able to retain up to 99.95% of the particles. These rooms, especially for immunocompromised patients,

surgical areas, areas for the preparation of parenteral drugs, etc., should have HEPA filtration and must also have a pressure differential to ensure that the air always goes from the cleanest to the most contaminated area.

Current regulations require that the design of the controlled environment areas be adapted to the needs of control and protection, establishing a classification, according to the danger that exists for the patient to be contaminated, from a slight risk to a very high risk. Likewise, It also establishes the obligation of annual validation and qualification of these rooms, contained in the UNE 171340:2020 Standard.

The combination of these elements and other purification elements, such as photocatalysis, electrostatic filtration and photocatalysis, electrostatic filtration or UV lamps, increase the efficiency of the systems and installations, to the point of providing systems and installations air free of microorganisms, to the treated areas in healthcare facilities [98-104].

In the case of SARS CoV-2, it is another biological agent that can be transmitted through airborne aerosols and, therefore, as with the other microorganisms, the three aforementioned protection mechanisms mentioned above are applicable to it [105-109].

Antibiotics and corticosteroids are frequently used in patients with COVID, and a new form of invasive aspergillosis called COVID-Associated Pulmonary Aspergillosis (CAPA) has been described [110-113]. It is recommended in some of these patients, isolation from adjacent areas and the use of supportive air purification equipment with high-efficiency HEPA filters, ultraviolet radiation lamps, and electrostatic filtration.

CONCLUSION:

Immunosuppressed patients admitted to hospitals are susceptible to contracting infections through the air, by different microorganisms (bacteria, fungi, viruses...) that can be common in the general environment, but that can produce in very sick people a nosocomial infection, with an impact, in many occasions irreversible.

The protection of the ambient air in hospitals is achieved through three fundamental ventilation, filtration and purification.

WHAT ARE THE MAIN AIRBORNE FUNGI THAT ARE POTENTIALLY PATHOGENIC TO HUMAN HEALTH?

Jesús Guinea

Invasive mycoses are serious opportunistic infections caused by fungi in hospitalized patients with varying degrees of immunosuppression. In general terms, the fungal kingdom is composed of yeasts and filamentous fungi or molds, the latter group being a series of species that multiply and proliferate by means of spores. These spores are airborne, and their accidental inhalation by high-risk patients can trigger the development of invasive mycoses that generally affect the lung locally and in some cases spread to other deep organs. This phenomenon is especially relevant in the hospital environment, which is where patients reside at times of increased risk for the development of invasive mycoses [114-117].

Considering the air as its natural vehicle, any spore-producing filamentous fungal species can be detected in the air. Without protective measures, the spores present in the air of the hospital environment will be a reflection of what is occurring in the street air [118, 119].

It is estimated that there are about 4 million species of fungi in nature, although only a few dozen are of clinical interest, being the species belonging to the genera *Aspergillus*, species of Mucorales, *Fusarium*, *Scedosporium* and *Pseudoallescheria*, the most relevant filamentous fungi. Aspergillus fumigatus is by far the filamentous fungus causing the greatest number of serious mycoses, known as invasive aspergillosis.

CONCLUSION:

The main filamentous fungi present in ambient air and capable of causing invasive mycoses in hospitalized immunocompromised patients are the various species belonging to the genera *Aspergillus*, *Mucorales*, *Fusarium*, *Scedosporium* and *Pseudoallescheria*.

WHAT PARAMETERS SHOULD BE MEASURED AND WHERE IN HOSPITALS AND HEALTHCARE CENTERS TO DEFINE THE QUALITY OF THEIR AMBIENT AIR? WHAT DOES OUR LEGISLATION SAY? IS IT HOMOGENEOUS IN ALL THE AUTONOMOUS COMMUNITIES?

Jesús Guinea

There is a relationship between the acquisition of invasive mycoses and the presence of filamentous fungal spores in the patient's environment. Indirect data suggest this relationship come from the disproportionate occurrence of aspergillosis cases in the form of hospital outbreaks when activities leading to high levels of spores in the air, such as renovation work, take place near areas where high-risk patients reside [120]. Similarly, the location of these same patients in areas equipped with high-efficiency HEPA protection is associated with fewer cases [121]. The most direct and clear evidence comes from the demonstration by means of molecular typing of the presence of the microorganism causing the infection in the air of the patient's environment [122,123].

Particulate counters are a quick and simple method to monitor the presence of airborne particles, but they simply alert of the presence of airborne particles, without discriminating between fungal spores or other particles (dust, pollen, etc.). For the specific detection of filamentous fungal spores, it is necessary to resort to the culture of air samples, which involves the aspiration of specific volumes of air and their subsequent culture in special media, identification, and calculation of spores per cubic meter of air sampled (CFU/m^3). The spore load tolerated in the air will depend on the level of protection

of the sampled area. While in street air spore levels of up to 10^5 CFU/m^3 are accepted, in unprotected areas of the hospital environment the presence of >25 CFU/m^3 has been defined as a risk threshold, while in those protected with HEPA filters the fungal levels should be 0 CFU/m^3 [124]. The regulations applicable to the hospital setting have not been very specific and are based on guides developed specifically for the design of operating rooms or of wider application in the hospital (Guía Práctica para el Diseño y Mantenimiento de la climatización en Quirófanos del Insalud; 1996 and Guía INSALUD 99 Verificación de Bioseguridad ambiental frente a hongos oportunistas; 1999). Therefore, in the absence of specific regulations, the centers where this type of sampling is carried out base their policy on the recommendations of scientific documents. Current scientific recommendations recommend air monitoring in rooms/protected areas, operating rooms, critical-burn patient units and oncohematology units [124]. CDC (Centers for Diseases Control and Prevention) recommendations recommend hospital air sampling both during periods of high risk due to construction work and periodic sampling to determine air quality, the effectiveness of barrier measures, or the condition of air conditioning systems [62]. Hospital centers such as the Gregorio Marañón Hospital apply a monthly sampling policy in protected environment areas, quarterly sampling in unprotected environment areas, and whenever there are high risk activities (construction sites) or within a hospital outbreak of invasive aspergillosis. This evaluates the integrity of filters, the detection of unknown spore niches, detects abnormally high levels of spores, and generates awareness of the problem among all hospital personnel responsible for air quality.

CONCLUSION:

Hospital ambient air quality is usually measured generally by particle counters and more specifically by counting per cubic meter the number of filamentous fungal spores. Acceptable quantities are different in different environments and in the case of operating rooms and neutropenic patient rooms a zero count is intended. Legislation on this aspect is not common either internationally or in Spain.

WHAT ARE THE MAIN DISEASES THAT CAN BE ACQUIRED IN A HOSPITAL DUE TO THE PRESENCE OF INADEQUATE AMBIENT AIR?

Patricia Muñoz García

Air is the medium through which a large number of infections are acquired, both inside and outside hospitals. This risk is especially high in hospitals and healthcare centers where fragile patients with a high risk of infection are concentrated, such as immunocompromised patients, elderly, operated, intubated patients, etc. These patients can acquire an infection either because of a general hospital air quality problem, to which this review is dedicated, or because of a specific failure of isolation and prevention of transmission of microorganisms from another patient, a visitor or a sick worker. Examples of these latter situations are the nosocomial transmission of respiratory infections such as influenza, chickenpox, respiratory syncytial virus, or even COVID-19 [113,125,126]. These cases must be recognized and avoided, since they cause significant morbidity and mortality.

However, as we were saying, the subject that concerns us are the diseases acquired by poor care of the aeration systems, which can constitute a hospital responsibility. Although this problem can cause different infections, the most paradigmatic is invasive aspergillosis, the most important clinical characteristics of which I will briefly describe. Aspergillosis is the name given to diseases caused by filamentous fungi of the genus Aspergillus, which is a ubiquitous microorganism that can be isolated from soil and dust and is universally distributed. It is characterized by producing small conidia, which, given their size, can be easily inhaled reaching the lung and paranasal sinuses, from where they can spread to any organ. The infection can also be acquired by direct inoculation in operated patients, when Aspergillus is in the air of an operating room [127].

Acute invasive aspergillosis usually affects immunocompromised patients, although the types of patients affected are becoming increasingly diverse [128]. The most frequent underlying diseases are hematological diseases (leukemia, lymphoma, progenitor transplantation), which account for almost 60% of cases in some series [129]. It is also described in other immunocompromised patients (solid organ transplants, HIV, high doses of steroids, solid tumors, etc.) and in patients with fulminant hepatic failure, advanced cirrhotics, critically malnourished patients, major burns, etc.

As the microorganism penetrates through the air, the most frequent invasive clinical forms in immunocompromised patients are pulmonary aspergillosis and rhinosinusitis. Less frequent are airway aspergillosis (obstructive bronchial, invasive tracheobronchitis, ulcerative or pseudomembranous), primary cutaneous, central nervous system (CNS) and disseminated aspergillosis. The invasiveness of the fungus is due to its great angioinvasive capacity and it can spread both by contiguity and by hematogenous route to organs distant from the primary infection, such as the CNS, liver, spleen, kidneys, prostate, etc. [130].

Pulmonary aspergillosis may begin asymptomatically and be a radiological finding or be accompanied by cough, fever, dyspnea, chest pain and hemoptysis. It is advisable to perform whenever possible a high-resolution chest CT scan, which usually provides more data than plain radiography and is a requirement in international diagnostic criteria [131]. The radiological manifestations considered suggestive of pulmonary aspergillosis are nodular lesions with or without a surrounding attenuation halo - halo sign (early), ca vitations and the air meniscus or crescent sign (later). However, aspergillosis can have other radiological presentations, especially in populations other than neutropenic patients. Early treatment (patients with halo or crescent sign) has been associated with longer survival than when treatment is initiated already with cavitation.

Tracheobronchial forms are more frequent in lung transplant recipients. Accepted clinical criteria require fibrobronchoscopy in which tracheobronchial ulcers, nodules, pseudomembranes, plaques or eschar should be observed. The diagnosis of sinusitis requires its radiological demonstration together with at least one of the following clinical data: acute localized pain sometimes radiating to the eye, nasal ulcer with black eschar or paranasal extension of the infection beyond the bony barriers and sometimes affecting the orbit.

The forms of invasive aspergillosis that appear in non-immunosuppressed patients associated with tissue damage, surgery or presence of foreign material are also extraordinarily important due to their clinical and legal significance. Some examples are post-surgical or post-traumatic keratitis or endophthalmitis, skin infections in burn patients, wound or surgical area infections, and those related to the placement of prosthetic valves, dialysis or central venous catheters, pacemakers, etc. [132-134].

Mortality of this infection is very high (around 60%), reaching more than 80% in very immunosuppressed patients, with CNS involvement or disseminated infection. At present, somewhat more satisfactory figures are obtained partly due to earlier detection and treatment with better tolerated and highly effective drugs.

CONCLUSION:

The paradigm of infection conveyed by poor quality ambient air in a hospital is Invasive Pulmonary Aspergillosis. It occurs in very vulnerable patients and with relatively small exposures, as in the case of neutropenic onco-haematological patients. On the other hand, it can occur in immunocompetent patients with massive exposures or by direct exposure of deep tissues and organs to ambient air, as in the case of infections acquired during extracorporeal surgery.

CAN ZERO INCIDENCE OF HOSPITAL-ACQUIRED INVASIVE MYCOSES BE ACHIEVED?

Patricia Muñoz García

The ambition to achieve zero incidence in various nosocomial infections is embodied in well-structured and ambitious campaigns, which have significantly reduced the incidence of catheter-related bacteremia, pneumonia in mechanically ventilated patients, surgical wound infections and even infections due to multi-resistant bacteria. It is therefore legitimate and very pertinent to try to approach zero incidence of hospital-acquired invasive mycoses.

As with many other infections, invasive mycoses diagnosed in the hospital may have been acquired in the community (food, plants, unfiltered air, dust) or in the hospital, and within the hospital, either in the area where the patient is admitted or during their movements around the center for tests or interventions. It is therefore difficult to establish the place of acquisition of aspergillosis [135]. On the other hand, there are many environmental factors (climate, wind, rain, vegetation, etc.) that can influence an increase in the number of specific cases. In addition, the problem is exacerbated by the fact that the incubation period of the disease is not well defined and depends on the immune status of the patient, the route of acquisition and the concentration of spores to which the patient has been exposed. We describe a well-documented case in which the time of infection could be determined and establish an incubation period of 15-20 days for our patient [122].

Despite these considerations and difficulties, it is imperative to try to detect hospital-acquired cases and prevent them through the strict implementation of general and specific measures. General measures include, among others, the following recommendations: Transfer of high-risk patients to a protected area distant from the construction or remodeling site and avoid exposure to plants, showers, contaminated food, etc; Keep doors and windows closed in areas with high-risk patients; Use of N95 masks by high-risk patients when leaving protected areas; Optimal isolation of construction sites with impermeable barriers; Reducing traffic through affected areas; Routine environmental measurements and in case of suspected nosocomial episode, to ensure that they do not exceed the levels allowed in each area; Optimal cleaning of surfaces with wet wipes and immediate removal of debris. Careful recording of filter changes; Follow-up of possible infections in patients at risk of IA; Regular meetings with all involved (infectious diseases, microbiology, preventive, hospital management, affected services, engineering) [124,136-140].

Specific measures include the administration of antifungal prophylaxis to patients at risk. This measure has to be directed only to patients with a very high risk, either because of their baseline conditions, or because they have been exposed to high levels of spores in the hospital, given that we are going to administer potentially toxic drugs to people who do not yet have the disease. But it is worth it, because these measures work.

As an example, I will give our experience with aspergillosis in a cardiac transplant program. In this population group the recommendation was to give prophylaxis to all patients, but we observed that, as long as there were no massive environmental exposures, only patients with certain risk factors suffered from aspergillosis. We defined which factors increased the risk and the duration of the increased risk in relation to each of the factors. With this we designed a prevention protocol in which we only administered prophylaxis to that particular group of patients and only for the minimum time necessary. In this way we managed to reduce the incidence of aspergillosis in our transplant program to zero for several years, with a very important impact on the overall survival of our patients and with good tolerance [141,142] . Figure 5 shows that in several years of the program there was not a single case, neither nosocomial nor community. Subsequently, a new nosocomial airborne contamination led to the appearance of nosocomial cases [132], which later disappeared again.

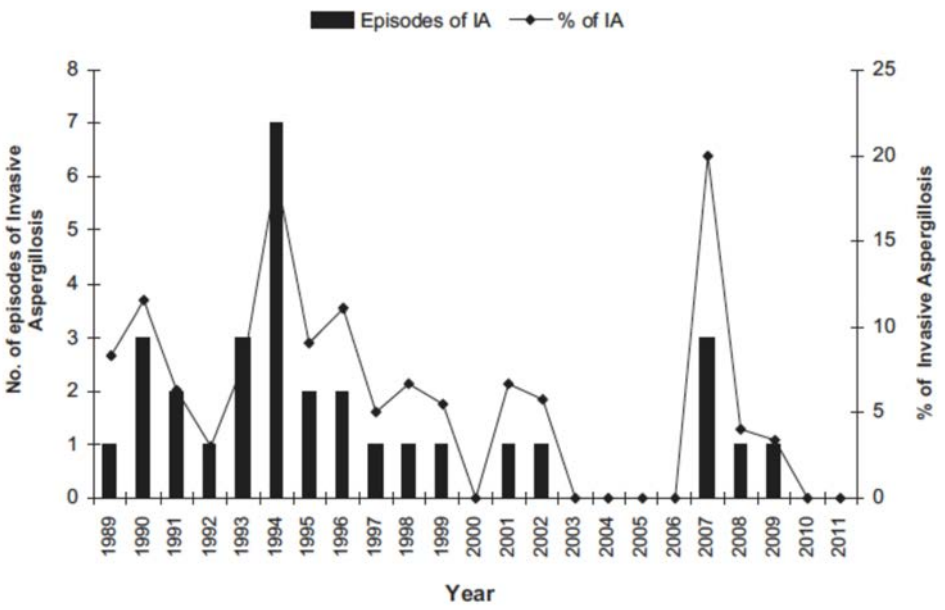

Figure 5 | **Annual distribution of cases of invasive aspergillosis in heart transplant recipients.**

It is necessary to insist on the need to be rigorous and exquisite in the observance of all prevention recommendations, including the measurement of spores in hospital air. We must be exemplary in the observance of the law on "zero tolerance" of spores in protected air (operating rooms, hematology) and not exceeding reasonable levels (25 ufc/m^3) in unprotected air [143]. This extraordinary care will mean that, unlike in many centers, we will not have to regret cases acquired in the operating room, which often complicate cardiac surgeries and lead to high mortality. Finally, if the episode could not be prevented, it is necessary to diagnose and treat it promptly and record it for subsequent analysis by all parties involved.

CONCLUSION:

Zero incidence of systemic mycoses in the hospital environment should be a reasonable goal and involves the implementation of a series of measures to protect the ambient air and sometimes also antifungal prophylaxis measures. We are not aware of the stable achievement of this objective, but the measures that have been tried have been associated with a clear decrease in the number of episodes.

WHAT IS THE CURRENT SYSTEM FOR MEASURING CONTAMINANTS, IS IT EFFECTIVE, AND WHAT MEASURES ARE MOST EFFECTIVE TO ENSURE GREATER SAFETY AND PREVENT DISEASE IN HOSPITALS AND HEALTH CENTERS?

Miguel Angel Gil Amigot

The Ministry for Ecological Transition and Demographic Challenge (MITECO) is the body in charge of collecting all the information and making an evaluation report annually regarding the values recorded in the environmental pollutant monitoring stations in each Autonomous Community (C.A.). This information is evaluated in relation to the legislation in force in Spain (Royal Decree 102/2011) which was constituted from the Directive 2008/50/EC on ambient air quality and a cleaner atmosphere in Europe. The evaluation is carried out according to the following criteria: the classification of the zone in relation to pollutant levels is determined by the highest value of each pollutant detected in the stations belonging to the zone [144,145].

The legislation establishes limit values that all Autonomous Regions must comply with in their air quality measurement zones. In the event that any Autonomous Region exceeds the legal limit values for a certain pollutant, it must take the necessary measures to reduce it to a permitted level. In addition, the legislation sets national target values for all Autonomous Regions to take measures and achieve a reduction of certain pollutants ($PM_{2.5}$, O_3, Cd...) for the specified year [146].

The World Health Organization (WHO) conducts global and European studies to analyze the impact of pollution on the health of the population. According to the results obtained, it is estimated that air pollution causes 3.2% of the world's illnesses and some 3.1 million premature deaths per year. The effects of pollution on health are mainly related to respiratory and cardiovascular diseases and cancer of the respiratory system. In Spain, the National Center for Environmental Health (CNSA) is the body in charge of controlling air pollution and carrying

out studies to contribute to the protection of people's health.

Due to the great impact of air pollution on people's health, healthcare centers, hospitals and health centers must adopt measures to control the indoor air quality level (IDA) of the centers. The air circulating inside healthcare facilities can be loaded with both small particles and gases from outside air and infectious bacteria and viruses exhaled by patients suffering from respiratory infections in the facility itself. Air conditioning and air ducts in healthcare facilities are essential elements for controlling the quality of the air that enters the facility and circulates within the hospital. In the case of air conditioning, the air coming from outside is filtered and acclimatized in the Air Handling Units (AHUs) and circulates through the air ducts to the different rooms. In the most sensitive areas of hospitals where the air quality must be optimal, i.e. in operating theaters and controlled environment rooms, current legislation regarding air conditioning requires compliance with certain requirements: a number of filtration stages, the application of filters with a high level of efficiency (HEPA filters), a permitted microorganism concentration and a minimum number of air renewals per hour.

In the rest of the hospital spaces, consultations, bedrooms, meeting rooms, general services, etc., less demanding requirements must be met in terms of air quality. From the point of view of the facilities, there are a series of important measures to be considered and adopted for the control of pollution in healthcare centers, as well as the use of the Air Treatment Units (AHU) and their maintenance, i.e. cleaning of the air conditioning units and air distribution ducts of the air driven by the AHUs, replacement of pre-filters and medium and high efficiency filters and checking the correct operation of the air conditioning system. In addition, continuous air renewal in all indoor spaces and window openings for supplementary ventilation are effective measures to reduce the transmission of respiratory infections.

CONCLUSION:

The most effective measures to ensure the quality of hospital ambient air is the establishment of filters in areas of maximum risk and for the protection of the most vulnerable patients.

WHAT ROLE CAN THE MEDIA PLAY IN THE DISSEMINATION AND AWARENESS OF THE GENERAL PUBLIC ABOUT THE PROBLEM OF AMBIENT AIR QUALITY AND IN PARTICULAR ABOUT PEOPLE WITH SOME TYPE OF RESPIRATORY DISEASE?

Javier Tovar García

Having established the importance and relevance of this problem for the present and future health of citizens, as well as its enormous repercussions on the sustainability of healthcare systems, we point out a group of considerations on the role that the media and journalism can and should play to mitigate these considerable effects and risks.

The media have a social responsibility to develop through good informative practices, distribution and dissemination capacity to reach the population, rigor and truthfulness of the contents and informative work to inform about the relationship between Health and Environment.

The role of the media in raising public awareness in order to value both the defense of health and a healthy environment is a crucial and essential part of their tasks.

Both health and environmental issues have acquired enormous importance for decades in the general and specialized media, beyond the very intense and specific media impact that the COVID-19 pandemic has generated since March 2020.

The conjunction of these two factors, preservation of a sustainable environment (in this case focused on achieving clean air) and the defense of health and well-being as a citizen's right, already has a certain presence in the media through news, reports, reports, debates, interviews and other types of journalistic content.

The Health/Sanitation and Environment sections occupy places in the newsrooms, although not with the resources and people that society demands; in addition, these departments have seen their staffs reduced as a result of the economic crisis that, since 2008, affected the media, both in the loss of revenue, the effects of the technological revolution and the bankruptcy of the business model.

It is necessary that, in the organization, structure and planing of media content strategies, the Environment and Health sections be strengthened and move towards greater coordination in order to offer joint informative production works that link and connect, with greater depth and breadth, the binomial Health/Environment.

In my opinion, the media have among their informative tasks to expose, both from the news and from the dissemination, rigorous, complete and contrasted, clear and truthful contents, of the reality that focuses and surrounds environmental pollution and its effects on health.

Issues, among others, such as environmental and health policies, and the connection between them; the denunciation of polluting situations of risk to health; the opinion of experts on this casuistry; the work, research and reports of both public and private organizations and institutions; giving a voice to those who suffer most directly from these problems; and other contents of social relevance, with specifics, examples, cases and stories that show and demonstrate the damage to health.

They must also complement the contents generated by the actors in the sector with their own initiative to offer quality information to society which, in turn, helps to alleviate the hoaxes and misinformation that are also produced in this area.

The protection of those who are especially harmed by air pollution, such as children, the elderly or people with respiratory diseases, must involve an added effort through content that gives visibility to reprehensible situations, measures or actions.

While it is true that the issue at hand, unlike other social or health problems, does not remain relegated or cornered in the media, I believe it is the responsibility of the media to increase its presence in prominent places on the journalistic agenda and in information showcases.

In addition, the media must be demanding in monitoring the actions of public authorities on the risks of pollution and its effect on health; monitoring compliance with standards and the strategies of industry and companies to collaborate in cleaner air, both in public and private spaces, workplaces, academics, hospitals or health centers, to give some examples.

It is also the role of the media to inject awareness and responsibility in citizens so that they commit, within the scope of their actions and decisions, to achieve clean air in homes and cities.

CONCLUSION:

The media must help to get out of the certain social numbness that leads the citizenship not to be really aware of the enormous health risks of breathing, day after day, unhealthy air that prevents our organism from functioning in a healthy way, and that acts as a kind of invisible killer that is difficult to detect and control.

WHAT ETHICAL ASPECTS WOULD YOU HIGHLIGHT? WHAT REFLECTIONS FROM THE PERSPECTIVE OF ETHICS ARE RAISED IN THIS PANDEMIC?

Diego Gracia Guillén

The current pandemic is new not only because it is produced by an agent different from all those known to date, but also because it is posing a new and unprecedented challenge to the health system. The latter was prepared to deal with epidemics of short duration, sudden onset and rapid end. In fact, that is what the term "epidemic" means. Dêmos is the Greek word for population, and epí is a prefix meaning over or through. To the essence of epidemic diseases belongs that they are transient and usually brief. In this they differ from endemic diseases, those in which the disease remains in a population for very long periods of time, reaching a certain degree of equilibrium between the germ and the populations it affects. The paradigmatic example of this is malaria, which has been so endemic in certain areas of the planet that its inhabitants have ended up developing certain genetic mutations that allow it to coexist with the parasite, as is the case of the modification of the hemoglobin cell that protects against malaria, even though it produces another disease, sickle cell anemia.

Epidemic diseases are characterized by their great aggressiveness, so that they affect very high percentages of the population, killing a large number of people and immunizing the rest. The immunity acquired during the epidemic prevents the germ from finding a place to reproduce, resulting in its disappearance.

All this is well known in medicine and something for which health systems, and with them advanced societies in general, are prepared. Crises are acute situations that require special measures, not only in health care but also in politics, economics, etc. The latter, for example, are aimed at maintaining economic activity by means of public subsidies to private companies and to workers who lose their jobs during the quarantine period, which in epidemics is, by definition, supposed to be short.

The current epidemic has two characteristics that make it peculiar. Firstly, it is a global epidemic, since it is the first, or one of the first, of the so-called "era of globalization" in which we find ourselves. The second characteristic is that it is lasting much longer than a classic epidemic. To such an extent that it is becoming so prolonged that it is beginning to have features more typical of endemics. This is something for which no one was prepared, neither the health system nor economic theory. When a pandemic begins to present symptoms typical of endemic diseases, as is the case in the present one, the social system as a whole enters into crisis. It was assumed that the advances in science, and more specifically in medicine, made the emergence of a phenomenon such as the one described impossible. As a result, what has happened has come as a surprise to everyone, and not exactly a pleasant one.

Medicine has played a fundamental role in the chronification of this epidemic. Left to its natural course, this disease would have very quickly infected a large part of the world's population, and after killing a certain percentage and immunizing the rest, it would have disappeared. That is the natural history of an epidemic disease. Chronification is the consequence of the preventive measures put in place by the political authorities in application of the principles of the preventivists. These measures undoubtedly save many lives, but at the price of delaying the immunization of the population, which is thus susceptible to infection for much longer, until all or most of the population is immunized, or until all or most of them are artificially vaccinated. The problem is that, in a pandemic, immunization has to reach all or most of the inhabitants of the earth, which poses all kinds of challenges for which our society is at present poorly and ill-prepared. The big question is whether the lessons learned during this crisis by the social system as a whole, and particularly by the health system, will serve to correct the enormous number of dysfunctions identified, or not. And this at all levels, from the local to the global.

The return to the "new normal" has become a slogan. Nothing could be more dangerous than this. If there is one thing we have to learn from this crisis, it is that we cannot go back to the past, so that this pandemic passes like a bad dream. We cannot go back to the past, because that will mean that we have learned nothing from this, which will leave the problems unresolved. This is not just about the profound reforms that the healthcare system requires. If what we are talking about is hygiene and public health, then many things have to change in people's habits and in the culture of society. Epidemic diseases are due to the Darwinian principle of the struggle for life of the different animal species, but they are also due to

the disruption of ecological balances. Historical epidemiology is a good witness to this cause. And the belief, so widespread today, that the human being is the king of creation and that everything else is at his service, so that he can use and abuse nature as he pleases, is a very serious error. Whoever does not treat nature, even inanimate nature, with respect, there is no reason to think that he will treat human beings with respect. And what is said about people is also true for companies and governments.

This crisis must be understood as a first warning that the path humanity is following is not correct, that it needs to be rectified, and that this must be rapid and profound. Otherwise, the warnings will follow one after the other, and they will become more and more serious.

CONCLUSION:

Ethics is the study of the correctness or incorrectness of the habits and customs of human beings. The present health crisis is not a mere fortuitous event, but a consequence of the way in which human beings are depredating nature and altering its equilibrium. It is necessary to promote a new culture of respect for nature and its balances, if only because it is the environment in which human life, our own life, is possible. In the face of a predatory culture, it is necessary to promote another based on respect and the maintenance of equilibrium. If this is not done, this pandemic will have been only a first warning, after which others, probably more serious, will follow.

TRANSPARENCY DECLARATION

For transparency purposes, we inform you that GSK has collaborated in the financing of this publication. Its contents reflect the authors' own opinions, criteria, conclusions and/or findings, which may not necessarily coincide with those of GSK. GSK always recommends the use of its products in accordance with the data sheet approved by the health authorities.

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Review

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COVID in Pediatric Age: an opinion paper

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ABSTRACT

The incidence of COVID in pediatrics was underestimated during the first months of the pandemic due to the oligosymptomatic nature of the infection in many children and the scarcity of diagnostic tests applied to this population. It is now accepted that children are infected and transmit the disease in the same way as adults. On the contrary, children have less severe and less lethal COVID, probably due to a lower maturity of the child's immune system, a lower number of ACE_2 receptors and the lower presence of comorbidities in this population group.

The development of a multisystemic inflammatory syndrome after SARS-CoV-2 infection in children, despite its rarity, is a very serious condition that frequently requires intensive care. Other less severe post-COVID manifestations have been described in children but are not yet well defined.

COVID has had and continues to have a significant psychological impact on the children themselves, on their caregivers and on the exacerbation of pre-existing psychiatric conditions.

We apply adult therapeutic principles to children but with very low levels of evidence. Information on the tolerability of the available medications in this population group is still scarce. The mortality of COVID in children is very low and generally affects children with significant comorbidities.

There are, at present, three vaccines licensed for pediatric use which are compatible with all other vaccines applicable to children.

In these circumstances, there has been much speculation about the indication for vaccination in the pediatric age group, but given its good tolerance, there are clinical and ethical reasons that, in our opinion, justify it.

Keywords: COVID-19, SARS-CoV2, treatment, vaccination, omicron, delta, ethics, inflammatory syndrome, pediatric population, pediatrics

COVID en la edad pediátrica: un documento de opinión

RESUMEN

La incidencia de COVID en pediatría ha estado infraestimada durante los primeros meses de la pandemia por el carácter oligosintomático de la infección en muchos niños y por la escasez de pruebas diagnósticas aplicadas a esta población. Hoy se admite que los niños se infectan y transmiten la enfermedad igual que los adultos. Por el contrario, los niños tienen cuadros clínicos menos graves y letales lo cuál parece relacionado con una menor madurez del sistema inmune del niño, una menor cantidad de receptores ACE_2 y la menor presencia de comorbilidades en este grupo de población.

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El desarrollo de un síndrome inflamatorio multisistémico tras la infección por SARS-CoV-2 en niños, pese a su rareza, es un cuadro muy grave que frecuentemente requiere cuidados intensivos. Se han descrito otros cuadros post-COVID en niños, menos graves, pero todavía no muy bien definidos.

La COVID-19 ha tenido y tiene un importante impacto psicológico en los propios niños, en sus cuidadores y en la exacerbación de cuadros psiquiátricos pre-existentes.

Aplicamos a los niños los principios terapéuticos de los adultos pero con niveles muy bajos de evidencia y la tolerancia de los medicamentos disponibles en este grupo de población es todavía mal conocida. La mortalidad de la COVID en niños es muy baja e incide generalmente en niños con importantes comorbilidades.

Hay, en el momento presente, tres vacunas autorizadas para el uso pediátrico y las vacunas frente a SARS-CoV-2 son compatibles con el resto de las vacunas aplicables a niños.

En estas circunstancias se ha especulado mucho sobre la indicación de vacunación en la edad pediátrica pero dada su buena tolerancia, existen, en nuestra opinión, razones clínicas y éticas que la justifican.

Palabras clave: COVID-19, SARS-CoV2, tratamiento, vacunación, ómicron, delta, ética, síndrome inflamatorio, edad pediátrica

INTRODUCTION

At the present time, in the midst of the expansion of the sixth wave of SARS-CoV-2 infection and its variant Omicron in Spain, the situation of COVID-19 in pediatric age group (under 18 years of age) is a matter of concern.

The Illustrious Official College of Physicians of Madrid (ICOMEM) has received different consultations regarding infection and disease in children and the COVID-19 Committee itself has had frequent discussions on this important population subgroup.

At the time of writing (January 17, 2022) PubMed responds to the query about articles containing the words COVID-19 or SARS-CoV-2 or Coronavirus in the title with the figure of 165,881 publications. When the pediatric age filter is introduced, 12,286 articles focus on pediatric age patients.

For all these reasons, we thought it appropriate to ask ourselves and try to answer a series of specific questions that are asked on a daily basis, not only by professionals related to the health sector, but also by the general population. Below we present the information we have been able to collect on this subject with the intention of providing the state of the art on different issues on the subject.

WHAT HAS BEEN THE REAL INCIDENCE OF COVID-19 IN PEDIATRICS?

At the beginning of the pandemic (2020), pediatric infection was thought to be less frequent than in adults, but the data in children during that period were probably underestimated [1], given the scarcity of diagnostic tests available at that time and the peculiarities of the COVID-19 in pediatrics [1].

For example, the prevalence of IgG antibodies against SARS-CoV-2 in a population-based sample in Spain in 2020 was lower in those under 20 years of age than that observed in the general population. Moreover, in them, the infection was very often asymptomatic (44.9%) [2], which facilitated that in clinical studies, it was under-diagnosed [3,4].

The most recent serological studies in symptomatic or asymptomatic children show that susceptibility to infection is similar in all age groups [5,6] and that the difference between them is due more to different behavioral habits than to other causes.

It is now recognized that children are infected and transmit the disease in a similar way to adults, although the actual incidence of SARS-CoV-2 infection in pediatrics is difficult to know exactly. European seroprevalence studies show that 15-31% of children under 12 years of age have been infected with the virus and this situation is increasing in recent months throughout Europe [7]. Initially affecting adolescents, it is now increasing preferentially in younger children, aged 5-11 years, who are not yet fully vaccinated. As of December 9, 2021, the incidence in Spain in children under 11 years of age was 533 cases per 100,000 inhabitants, the highest of all population groups and almost 4 times higher than that of persons over 80 years of age [8].

WHAT HAVE BEEN THE REASONS FOR LOWER DISEASE SEVERITY IN THIS POPULATION?

There is evidence-based consensus on the lower severity of COVID-19 in children and adolescents. The lower maturity of the immune system makes children more vulnerable to certain infections [9], but it may also make less likely the proinflammatory state that is associated with much of the morbidity and mortality observed in COVID-19. [3,10]. On the other hand, the expression of the ACE_2 receptor, to which SARS-CoV-2 binds, is lower in children [9,10], who also tend to have been exposed to environmental toxins and tobacco for a shorter time than adults, which increase the expression of these receptors [11]. Having fewer receptors to which the virus binds would make children less susceptible to severe infection, and less prone to a proinflammatory response. Finally, the lower prevalence of comorbidities and risk factors associated with worse outcome (obesity, diabetes and hypertension among others) may also explain the lower severity of COVID-19 in pediatric age [12-15].

WHAT DO WE KNOW ABOUT TRANSMISSIBILITY OF SARS-COV-2 INFECTION IN CHILDREN?

During the course of the epidemic, we have learned that the capacity of children to become infected, to generate viral loads in the upper respiratory tract and to transmit viruses is

comparable to that of adults [5]. The greater biological transmissibility of the latest strains, already evident in the delta and notably in the omicron, has highlighted the vulnerability of children to infection and their role as transmitters. The lower vaccination rate in this age group may have marked the differences in incidence compared to adults.

The airborne route, in the home, seems to be the main source of infection and transmission [16,17]. In schools, mainly the younger children's classes, have not been the focus of major epidemic outbreaks and, in fact, the outbreaks described at the beginning of the pandemic showed more involvement of infected teachers in the origin of the secondary cases than of the student body [18].

As age increases, transmission behavior becomes more similar to that of adults, and the lack of school-based prevention measures also increases the rate of transmission in this environment.

Vertical transmission is a mechanism of transmission in the newborn and during breastfeeding, although it seems to carry a low risk of transmission [19].

WHAT IS THE SYMPTOMATOLOGY OF COVID-19 IN CHILDREN?

Symptoms, respiratory support therapy requirements and evolution vary depending on whether we are dealing with a general casuistry or if we specifically review data from children and adolescents, collected in emergency departments and hospital records, but the figures are very concordant when the circumstances are similar [20-22].

The symptoms in children, in addition to fever, are respiratory symptoms, cough, pharyngeal erythema and rhinorrhea, but also fatigue, vomiting and diarrhea, and alterations of taste and smell. It is necessary to take into account the possibility of renal, cardiovascular, neurological, cutaneous, hematological, hepatic and ocular alterations [23].

In one of the first systematic reviews of the literature published in 2020, 90% of cases in children corresponded to asymptomatic, mild or moderate forms and only 6% of cases were severe or critical [20]. Only 2 to 5% showed oxygen saturation of less than 92%, although imaging tests revealed 18% of pneumonias and 80% of the CT scans performed showed alterations. The results reported in a cohort of 582 children with a confirmed diagnosis of COVID-19, of whom 13% were recruited in primary care and the rest in hospital institutions of different levels, are of great interest, as this is a European multicenter study with broad Spanish participation. Sixteen percent were asymptomatic and although 62% were admitted, only 12% could be considered severe as they required some type of respiratory support treatment and only 5% required admission to the ICU. Mortality was 0.69% [24].

These data were confirmed in reviews throughout the development of the pandemic and already in a study carried out in a pediatric population of 135,794 subjects, 5,374 cases were found, of which 5,015, more than 90%, were asymptomatic or had mild symptoms. Seven percent were hospitalized and of these 28% were admitted to the ICU and 9% required invasive mechanical ventilation. Overall mortality was 0.2%. [25].

The data do not differ much from those found in studies with smaller numbers of cases, but limited to children requiring emergency department care. In a study of 422 children seen in an emergency department, 78 cases of SARS-CoV-2 infection were found, of which 87% were asymptomatic or mild cases, 13% were moderate and only 1.2% were considered severe [26]. In this study, 7.7% of the children required oxygen therapy, 1.3% CPAP treatment and none required invasive mechanical ventilation, with no deaths.

With respect to severity risk factors leading to hospitalization with or without admission to the ICU, age under 2 years, comorbidity and the presence of onco-haematological disease seem to be associated with greater severity [27,28]. In the aforementioned European multicenter study [24], in addition to comorbidity and younger age, the presence of pneumonia at the time of diagnosis was also a higher risk factor.

WHAT HAS BEEN THE INCIDENCE AND CLINICAL MANIFESTATIONS OF POST-COVID-19 MULTISYSTEMIC INFLAMMATORY SYNDROME (MIS-C) IN CHILDREN?

Pediatric Multisystem Inflammatory Syndrome (MISC-C, MIS-C) is a rare and severe post-infectious complication of SARS-CoV-2 infection that mainly affects children and adolescents. It is defined by WHO as an illness in a pediatric-aged patient (0 to 18 years) presenting with fever for a period ≥ 3 days, with elevated biomarkers of inflammation (CRP, ESR or procalcitonin) and with at least two clinical signs of multisystem involvement. Such signs include: rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation (oral, hands or feet), hypotension or shock, cardiac dysfunction, pericarditis, valvulitis, coronary anomalies , elevated troponin/BNP, evidence of coagulopathy or acute gastrointestinal symptoms (diarrhea, vomiting or abdominal pain), with no other obvious microbial cause of inflammation (including bacterial sepsis or toxic shock syndrome) and with evidence of previous SARS-CoV-2 infection [29].

Data on incidence are limited. In a cohort study of 248 persons with MIS-C in U.S. children under 21 years of age, the incidence was 316 persons/10^6 SARS-CoV-2 infections. In addition, the adjusted incidence estimate was 5.1 cases/10^6 person-months [30]. Incidence did not differ significantly by sex, but was significantly lower in persons aged 16-20 years compared with children aged 5 years or younger. The incidence was 9 times higher among Blacks, Hispanics, or Latinos and 3 times higher among Asians or Pacific Islanders [30].

Regarding clinical manifestations, several systematic reviews have been published including studies on MIS-C that have provided an overview of the clinical signs, laboratory findings, imaging test characteristics, treatments and out-

comes of patients with MIS-C [31-34]. It generally has a heterogeneous clinical spectrum and none of the clinical manifestations or signs appear to be sensitive or specific for MISC [32]. The median age of those with the disease is 8 years. Fever is present in almost all cases and gastrointestinal symptoms are predominant (65-90%), mainly abdominal pain (58-73%), vomiting (57-68%) and diarrhea (50%). Cardiac involvement is frequent (79%) with tachycardia (76.7%), myocarditis (41.4%) and mild or moderate decrease in left ventricular ejection fraction (LVEF between 30 and 55%; 40%) [31]. Echocardiographic abnormalities are found in more than half of the cases, the most common being a depressed left ventricular ejection fraction (LVEF) (45.1%) [32]. Half of the patients present cardiogenic shock and severe cardiovascular complications such as LVEF below 30% (7%), coronary dilatation (11.6%) and aneurysm formation (10%) [31]. Overall, 30-50% of MIS-C sufferers have respiratory symptoms, including upper respiratory tract symptoms (24%), dyspnea (27%) and multiple radiological infiltrates (26-55%) [32]. Non-purulent conjunctivitis (47-82%) and skin eruptions (57-74%) such as rush or polymorphous exanthema (55%) are frequently observed [31].

MIS-C cases present with significant laboratory abnormalities: neutrophilia and lymphopenia, significantly elevated cardiac markers (troponin and brain natriuretic peptide), increased inflammatory biomarkers (C-reactive protein, procalcitonin, ferritin, interleukin-6), and substantially increased coagulation markers, including D-dimer and D-lymphopenia [31-35].

The clinical manifestations of patients with MIS-C vary according to age. Younger children (0 to 4 years), present a lower proportion of severe manifestations and fewer admissions to the ICU, with more frequent conjunctival findings, skin rash and abdominal pain [34,35]. Patients aged 18 to 20 years were more likely to have pneumonia, dyspnea, myocarditis, and cardiac dysfunction [31,34,35].

The onset of MIS-C follows peaks of SARS-CoV-2 infection, with a median of 4 weeks (range 2 to 5 weeks) and usually following asymptomatic or mildly symptomatic COVID-19 cases [36]. Despite the potential severity of the disease, with two-thirds of patients requiring ICU admission for a median of 5 days (range: 4-8 days), most recover with a fairly low reported mortality rate (1.3-2%) [31-33,35,36]. Death usually results from shock and/or myocardial dysfunction.

Although MIS-C has clinical features in common with Kawasaki disease or toxic shock syndrome and half of the patients with MIS-C meet the diagnostic criteria for these conditions, they are distinct entities [37-41].

IS THERE A PEDIATRIC POST-COVID-19 SYNDROME?

There is increasing evidence and knowledge of post COVID-19 syndrome in adults, initially described in Italy [42] and later in China (Wuhan) in which they found that up to 76% of cases can be symptomatic 6 months after diagnosis [43]. This is not the case in pediatrics, where data are, even today, scarce to be able to define and diagnose post-COVID-19 syndrome or prolonged pediatric COVID-19. We do not know its incidence, disease burden or long-term sequelae. First pediatric cases described (year 2021) [44] are a series of 5 Swedish children, mean age 10.4 years, with symptoms similar to adult post-COVID-19 syndrome, who persist symptomatic 2-6 months after acute infection. More recent studies include cohorts of children with prolonged post-COVID-19 sequelae in Italy [45], Sweden [44], Russia [46], Spain [47] and the United Kingdom [48]. They share as risk factors for developing this post-COVID-19 syndrome, having a history of allergic diseases and being older than 6 years. The most frequently reported characteristics are: age between 10.4 and 12 years, fatigue, dyspnea, chest pain, difficulty concentrating and sleep disturbances that persist for several months after the acute infection. Management is not clearly protocolized and treatment is symptomatic.

Prolonged follow-up of symptomatic children by specialized multidisciplinary teams (physicians, physical rehabilitators, psychologists and psychiatrists) is important in order to better understand the disease and the care and social needs it may generate.

Several groups are proposing novel forms of monitoring [49] and care of these patients, grouping patients and resources in specialized units [50]. It is essential to have a good knowledge of this new pathology and to be able to foresee the care and social needs derived from it and its future long-term evolution.

WHAT IS THE REAL PSYCHOLOGICAL IMPACT OF COVID-19 ON CHILDREN?

Children are not immune, nor are they indifferent, to the adverse psychological effects of the pandemic and quarantine measures. Children as young as 2 years old are aware of the changes around them and are affected by them [51]. The child/youth population is not only afraid of infection, but is also very concerned about the consequences it may have on their families. Adolescents are also concerned about the interruption of their studies [52], limitations in their personal relationships, etc. Many studies have focused on the psychological consequences in this age group (depression, stress, anxiety, inattention, irritability, etc.) as well as on the aggravation of previous psychiatric diseases. In a meta-analysis by Panda et al. [53] the authors divided the studies on the subject into three categories: those on previously healthy children/adolescents, those on children with pre-existing behavioral comorbidities and, finally, those on the impact on caregivers confined to the children at home/hospital.

In the group of healthy children, the work of Duan et al [52] shows that anxiety levels are very high in both adolescents and younger children, but depression is higher in adolescents, mainly determined by factors such as addiction to the Internet and smartphones. In our environment, in a survey conducted

in Spain and Italy [54], on the impact of confinement on the 3-18 years age group, the authors report that the most frequent problems were: difficulty concentrating (76.6%), irritability (39%), boredom (52%), restlessness (38%), feeling lonely (31%), nervousness (38%), discomfort (30%), worries (30%), anxiety (28%), anger (25%), apathy (24%), sadness (23%) and fear (23%). These data are very similar to those found in other studies [53].

Positive reinforcement and healthy emotional interaction among family members is a simple but effective measure to alleviate stress, although many will need psychological intervention.

In those with pre-existing psychiatric problems, there is a high likelihood of worsening of their behavioral symptoms [53,55]. To mitigate this negative impact, it is necessary to apply multifaceted, age- and developmentally appropriate strategies to be taken by health authorities.

In the third category, regarding confined caregivers, 52.3% and 27.4% developed anxiety and depression, respectively, when isolated with the children [56,57].

WHAT IS THE CORRECT PHARMACOLOGICAL TREATMENT OF COVID-19 IN CHILDREN?

There are no data from randomized clinical trials to establish firm recommendations on the optimal pharmacological treatment of COVID-19 in pediatric patients. For this reason, recommendations are largely based on efficacy and safety data obtained in adults and on the risk of disease progression in children [58,59]. It seems reasonable to follow the recommendations made for adults the older the child is or the more severe the disease.

However, as pandemic waves have occurred, experience has been gained in the treatment of children that allow reasonable recommendations to be made, which vary according to the clinical picture:

1.- Children with mild disease that does not require hospitalization. In most cases the administration of symptomatic and supportive treatment is sufficient.

2.- Children with moderate or severe disease requiring hospitalization. In this case, the administration of the following may be considered:

- Remdesivir: is approved for children >12 years and weighing >40 kg. It is also available under an FDA Urgent Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing between 3.5 kg and <40 kg or who are less than 12 years old and weigh more than 3.5 kg. [60]. It could be recommended for all hospitalized children requiring oxygen therapy, regardless of age and weight, with less than 7 days of symptoms [61]. The recommendation is strongest for children >12 years with need for oxygen therapy and who have risk factors for disease progression to severe forms and for children >16 years with need for oxygen therapy, even if they do not have risk factors for progression [62]. In most cases the evolution is good without the need to initiate treatment with remdesivir.

- Dexamethasone: would be recommended in children requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [63]. Given the efficacy of its treatment in adults, its use in children requiring oxygen therapy and who have pneumonia has been widely extended.

Other drugs approved and recommended in adults, such as other antiviral drugs, immunomodulators (tocilizumab, sarilumab, anakinra) or drugs with anti-inflammatory activity (baricitinib, tofacitinib) lack information to be able to recommend their routine use in children. Tocilizumab has been the most commonly used immunomodulator in critically ill patients, generally in intensive care units, especially if elevated IL-6 levels are confirmed. Both tocilizumab and baricitinib are currently being evaluated in clinical trials in children.

3.- Children with multisystemic inflammatory syndrome (MIS-C). There are only data from observational studies. Hemodynamic and respiratory support treatment is a fundamental therapeutic tool. Intravenous immunoglobulins and/or steroids are used as first-line treatments [64,65]. In some refractory cases, IL-1 (anakinra) or IL-6 (tocilizumab) inhibitors have been used successfully [66]. The best option or appropriateness of combination therapy is unknown, although some studies have shown greater benefit from co-administration of immunoglobulins and steroids than immunoglobulins alone [67].

4.- Children with underlying disease at high risk for severe disease. There are no data to support the use of neutralizing monoclonal antibodies or antiviral drugs in children who do not require hospitalization but who have risk factors for progression to severe disease [68]. In these cases, use could be considered, especially in cases with more than one criterion or age >12 years. In fact, bamlanivimab + etesevimab, casirivimab + imdevimab and sotrovimab have been approved for use in high-risk children aged >12 years and weighing >40 kg. It is important to note that only the monoclonal sotrovimab has been shown to be effective for the omicron variant. At present time, there is very limited availability of these drugs in Spain, which must be requested through the AEMPS. Remdesivir has been tested in a clinical trial of early administration, although only 1.4% of patients were between 12 and 18 years of age [69], however, the use of 3 doses on an outpatient basis in patients at risk could be considered as an option.

WHAT IS THE MORTALITY RATE OF COVID-19 IN THE PEDIATRIC AGE GROUP?

It is not easy to provide data on the mortality of the disease, which has also been changing as time has passed in the pandemic. Of 24,778 deaths from any cause quantified as excess over the expected deaths that occurred in Spain up to June 2020, there were only 65 deaths in children under 19

years of age [70]. It should also be noted that in the population base of the English National Health System there was no excess mortality in the pediatric population in 2020 that could be attributed to SARS-CoV-2 infection [71].

About 1% of infected children require hospitalization, less than 0.02% require intensive care, and mortality is very low. Generally, occurs in children with comorbidities [72].

In a review carried out by the Committee of Evidence-Based Pediatrics of the Spanish Association of Pediatrics and the Spanish Association of Primary Care Pediatrics, it is established with a low level of evidence that mortality in pediatric patients admitted for COVID-19 is 413/100.000 patients and, in series that also include non-hospitalized patients, from 104 to 208/100,000 cases. Most of the deaths are due to complications of serious chronic diseases, and the direct causality of COVID-19 is unclear [73].

The estimated mortality in the pediatric population in a recent systematic review is 0.12% [4], sharply lower than that of the general population of 2.22% worldwide in February 2021 [74].

Factors related to ICU admission (46.3%) were age, fever, multisystem inflammatory syndrome (MIS-C) and seizures [75].

WHAT ARE THE REASONS FOR THE PROPOSAL OF VACCINATION IN THE PEDIATRIC AGE GROUP?

Vaccination in the pediatric age group responds to the common pandemic vaccination response. It has benefits both for the potential pediatric patient with COVID-19 and for society as a whole. From the individual point of view, although the risk of severe COVID-19 in the child is lower than in the adult [76,77], vaccination would further reduce this possibility, even from a theoretical point of view due to new circulating variants. Therefore, a first benefit would be the reduction of severe infection. Also, in the case of symptomatic infection, the vaccinated child's recovery should be much faster, which would bring as a second benefit the reduction of the period of non-schooling or, at least, of the time in which socialization would not be possible due to isolation after infection by SARS-CoV-2. As a third benefit, derived from the previous one, a better mental health would be achieved [78]. Also, since the immune response is more efficient and longer lasting in children than in adults, including the humoral response, vaccination at this age would generate a higher quality response [79].

At the collective level, vaccination of children would increase the vaccination rates of the entire population in general and, therefore, of the so-called herd immunity. It would limit the possibilities of transmission between children and drift towards severe disease, and from child to adult, also reducing in this group the probabilities of acquisition of COVID-19.

Since the selection factor for new variants lies in the number of people infected with SARS-CoV-2, broad vaccination of this group would reduce the likelihood of the emergence of new variants [76]. Also, the absence of new variants would allow to maintain the current diagnostic strategies (antigen test, PCR, serology, ...) since modifications would not be necessary.

WHAT IS THE VACCINE EFFICACY AND SAFETY OF VACCINES IN CHILDREN?

At present there are 3 vaccines available for vaccination of children and adolescents. In young children (5 - 11 years) only the vaccine Comirnaty 10 mcg/dose (Pfizer & BioNTech) is licensed [80,81]. In older children and adolescents (12-17 years), Comirnaty 30 mcg/dose (Pfizer & BioNTech) and Spikevax (Moderna) are used [80].

These vaccines contain a messenger RNA molecule that facilitates the production of the virus spike protein; it is recognized by the immune system, generating an antibody response against SARS-CoV-2.

The vaccines approved in the pediatric age group have demonstrated high immunogenicity and safety in phase 3 clinical studies. Their effectiveness in preventing severe symptomatic forms of disease and lethality is expected, although long-term effectiveness data are lacking.

The dose administered in children aged 5-11 years is one-third of that received by adults, because their antibody response to SARS-CoV-2 at the 10 µg dose was similar to that seen in 16- to 25-year-olds at the 30 µg dose.

They are administered in the deltoid muscle with a schedule of two doses separated by at least 8 weeks. The patterns are different in immunosuppressed children or those under immunosuppressive treatment [82].

Other vaccines are under development in clinical trials in this age group and may be licensed in the future.

HOW ARE THE USUAL VACCINES COMPATIBLE WITH THE SARS-COV-2 VACCINE IN CHILDREN?

The Interterritorial Council of the Spanish Government published on December 7, 2021 the recommendations for vaccination against COVID-19 in children aged 5-11 years [83].

Childhood vaccination against SARS-CoV-2 has been included for the first time in the Children's Systematic Vaccination Calendar of the Spanish Association of Pediatrics 2022 [82].

Although there is insufficient data on co-administration with other vaccines, given their characteristics and mechanism of action, it is expected that there will be no incompatibility with the vaccines of the children's calendar. They can be administered simultaneously (in the same medical visit) as the rest, or sequentially (on a different day), always respecting the rules of administration (different anatomical site, syringe and needle). It is not necessary to respect a certain time between COVID-19 vaccines and any other vaccine of the calendar.

There is recent information recommending the interval to be respected between previous SARS CoV-2 infection and the administration of the vaccines, which is at least 8 weeks for children aged 5-11 years, and 4 weeks for adolescents aged 12-17 years.

There is no data on the interchangeability of the authorized mRNA vaccines, so in primary vaccination it is recommended to use the same vaccines. In patients under treatment with other biological products (convalescent plasma or monoclonal antibodies) it is recommended to delay the vaccine for 3 months.

In case of special situations: immunosuppression, allergy, etc., the vaccination of each patient will be assessed individually [82].

WHAT IS THE EXPECTED IMPACT OF ANTI-COVID-19 VACCINATION IN CHILDREN ON COMPLIANCE WITH THE SCHOOL CALENDAR?

During the first wave of the pandemic (until September 2020), school closures and their impact on the mental health of schoolchildren have been reviewed by Viner et al. [84]. The authors searched 11 databases and identified 36 studies on the subject in 11 countries, with a total of 79,781 children and adolescents. The duration of school closure ranged from 1 week to 3 months. The studies reported a relationship between school closure and mental health disturbances and health behaviors among children and adolescents [84,85].

In Spain, López-Bueno et al. have also reported the consequences of school closure with not only socio-affective alterations but also a decrease in physical activity in schoolchildren and excessive exposure to screens [86]. Consequences such as weight gain in schoolchildren have been demonstrated [87], the progression of myopia [88, 89] and the increase in sedentary lifestyles [90].

On the other hand, school closures have not been shown to clearly decrease transmission and therefore, at the present time, it appears that the advantages of keeping schools open outweigh the disadvantages [91].

An ECDC modeling study has shown that vaccination of children aged 5-11 years in a country like Spain, with high adult vaccination rates, can reduce transmission by up to 15%. Therefore, the vaccination schedule of the Spanish Association of Pediatrics (CAV-AEP) believes that restoring normal school life to children is a priority objective, which has a direct impact on their health, and can only be achieved through childhood vaccination [82].

WHAT ETHICAL ISSUES ARE RAISED BY COVID-19 IN CHILDREN AND ITS PROPHYLACTIC AND THERAPEUTIC MANAGEMENT?

The ethical considerations of vaccination in this age group are supported by an assessment of the direct and indirect effects that the COVID-19 pandemic has had and continues to have on the health and well-being of children [92]. The relatively low risk posed by acute COVID-19 in children, accompanied by the small but existing uncertainty about the relative harms of vaccination and disease, make the risk-benefit balance of vaccination in the pediatric age more complex [93].

In this sense, the direct benefits are clear, if safe and effective vaccinations such as the current ones can prevent deaths and serious illness in children, there is a clear ethical justification for vaccination. Indirect benefits would also support such a justification and include protection of others through reduced spread, reduced overall stress on children from school closures and social distancing, and reduced economic cost to families.

Thus, the main ethical arguments in support of COVID 19 vaccination include the following [92-95]:

1. Consistency in relation to respect for autonomy. Generally, when the range of risk is narrow, the decision is a matter of personal choice. Between the two risks, which one should caregivers choose? Current evidence suggests that the risk of refusal of childhood vaccination is greater than the risk of vaccinating children against COVID-19.

2. Local justice. Children from low socioeconomic and ethnic minority backgrounds are especially prone to COVID-19 morbidity and the harms of social distancing. Vaccination could mitigate these disparities.

3. Global justice. The greater the number of people vaccinated, the closer the society is to herd immunity and protection of the most vulnerable in it. Delaying vaccination of children can hinder recovery from the pandemic and can deepen socioeconomic gaps.

4. Utilitarian considerations. Currently, a major concern is the emergence of mutations. When adults are already vaccinated, selection pressure will operate in a pediatric reservoir, thus cultivating variants that spread among children, and even undermine herd immunity.

Therefore, it would not be fair to deprive the child population of the benefits of vaccination, which are already enjoyed by those over 12 years of age (although the health objectives are different) [82]. Children's access to the vaccine is a public responsibility and the final choice is a matter of pediatric informed consent.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Nuevos modelos predictivos de bacteriemia en el servicio de urgencias: un paso adelante

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RESUMEN

La atención de pacientes con sospecha de un proceso infeccioso en los servicios de urgencias hospitalarios(SUH) se ha incrementado en la última década hasta suponer alrededor del 15-20% de todas las atenciones diarias. En la valoración inicial de estos enfermos se toman muestras para los distintos estudios microbiológicos en un 45% de los casos, donde predomina la obtención de hemocultivos (HC), en el 14,6% de todos ellos. La rentabilidad diagnóstica de estos HC es muy variable (2-20%). Los focos o procesos infecciosos más frecuentes sospechados o confirmados de las bacteriemias verdaderas(BV) en los SUH son la infección del tracto urinario (45%) y la infección respiratoria (25%). Por todo ello, la sospecha y confirmación de la BV tiene un relevante significado diagnóstico, pronóstico y obliga a cambiar algunas de las decisiones más importantes a tomar en el SUH. Entre otras, indicar el alta o ingreso, extraer HC y administrar el antimicrobiano adecuado y precoz. La intención de esta revisión es poner de manifiesto las evidencias científicas publicadas en los últimos cinco años, aclarar las controversias existentes actuales y comparar la capacidad para predecir bacteriemia de los últimos modelos predictivos publicados desde el año 2017 con los ya existentes en esa fecha, año en el que se publicó una revisión que dejaba abierta la propuesta de seguir buscando un modelo con un rendimiento adecuado para los SUH. Y así, a partir de ella, generar distintas recomendaciones que ayuden a definir el papel que pueden tener estos modelos o escalas en la mejora de la indicación de obtención de los HC, así como en la toma inmediata de otras decisiones diagnóstico-terapéuticas (administración precoz y adecuada del tratamiento antibiótico, solicitud de estudios complementarios y otras muestras microbiológicas, intensidad del soporte hemodinámico, necesidad de ingreso, etc.)

Palabras clave: Servicio de urgencias, Bacteriemia, Modelo predictivo, Hemocultivos, Biomarcadore,. Procalcitonina.

New predictive models of bacteremia in the emergency department: a step forward

ABSTRACT

The care of patients with a suspected infectious process in hospital emergency department (ED) has increased in the last decade to account for around 15-20% of all daily care. In the initial evaluation of these patients, samples are taken for the different microbiological studies in 45% of the cases, where obtaining blood cultures (BC) predominates, in 14.6% of all of them. The diagnostic yield of these BC is highly variable (2-20%). The most frequent suspected or confirmed foci or infectious processes of true bacteremia (TB) in the ED are urinary tract infection (45%) and respiratory infection (25%). For all these reasons, the suspicion and confirmation of TB has a relevant diagnostic and prognostic significance and requires changing some of the most important decisions to be made in the ED. Among others, indicate discharge or admission, extract BC and administer the appropriate and early antimicrobial. The intention of this review is to highlight the scientific evidence published in the last five years, clarify the current controversies and compare the ability to predict bacteremia of the latest predictive models published since 2017 with those already existing on that date, year in which a review was published that left open the proposal to continue searching for a model with adequate performance for ED. And so, based on it, generate different recommendations that help define the role that these models or scales can have in improving the indication for obtaining BC, as well as in the immediate making of other diagnostic-therapeutic decisions (administration early and appropriate antibiotic treatment, request for complementary

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studies and other microbiological samples, intensity of hemodynamic support, need for admission, etc.)

Keywords: Emergency department, Bacteraemia, Clinical prediction rule, Blood cultures, Biomarker, Procalcitonin.

INTRODUCCIÓN

Impacto de la infección grave en el Servicio de Urgencias Hospitalario. La atención de pacientes con sospecha o confirmación de un proceso infeccioso en los servicios de urgencias hospitalarios (SUH) españoles se ha incrementado significativamente en la última década hasta suponer alrededor del 15-20% de todas las atenciones diarias en estos dispositivos [1,2]. Además, la gravedad de su presentación clínica (aquellos que cumplen criterios de sepsis, pacientes con comorbilidad relevante, inmunodeprimidos, ancianos o ante la sospecha de bacteriemia) y la mortalidad intrahospitalaria y a corto plazo (30 días), también han sufrido un incremento en la última década [1,2]. Incluso, durante el último año donde los SUH se han visto muy presionados por la pandemia de COVID-19 [3], tanto estos pacientes como los atendidos por infección bacteriana han aumentado su tasa de ingresos, la necesidad de cuidados intensivos y la mortalidad a corto plazo [4].

Obtención de hemocultivos y confirmación de bacteriemia verdadera desde el Servicio de Urgencias Hospitalario. En la valoración inicial de estos enfermos, en el propio SUH, se toman muestras para los distintos estudios microbiológicos hasta en un 45% de los casos [1,2]. Entre ellos predomina la obtención de hemocultivos (HC), que se lleva a cabo en el 14,6% de todos los pacientes atendidos con sospecha o confirmación de infección en los SUH [1,2,5]. Aunque, al contrario de lo que se podría suponer, se ha comunicado una menor tasa de solicitudes de procesamiento de HC desde los SUH en el año 2020 y, junto a ello, de aislamientos [6].

Se define como bacteriemia la presencia de bacterias en la sangre, que se pone de manifiesto por el aislamiento de éstas en los HC [7,8]. A pesar de las nuevas técnicas de detección rápida (del ADN del patógeno o por aplicación de espectrometría de masas, entre otras) [7-10], los HC permiten el diagnóstico etiológico de la infección, aportan información sobre la sensibilidad del microorganismo y favorecen la optimización del tratamiento antimicrobiano [7-11].

La rentabilidad diagnóstica de estos HC es muy variable (2-20%) [5,12-16], mientras que los considerados "HC contaminantes" pueden alcanzar incluso tasas del 30-50% de los aislamientos [6,13,15]. Por otro lado, los HC con aislamiento significativo en pacientes dados de alta desde urgencias (ASPAU) pueden representar un 3-5% de los extraídos en el SUH [13,15]. Estos hechos representan verdaderos problemas, al conllevar un incremento de las pruebas diagnósticas realizadas, la estancia hospitalaria, los costes y la administración de tratamientos antibióticos innecesarios o, en su caso, altas improcedentes en los casos de ASPAU [15-19].

La incidencia de bacteriemia comunitaria ha aumentado hasta 2 de cada 1.000 atenciones en los SUH españoles y a 10 episodios por cada 1000 ingresos hospitalarios desde estos dispositivos [5,6,12,13].

Epidemiología, etiología y relevancia de la bacteriemia. Los focos o procesos infecciosos más frecuentes sospechados o confirmados de las bacteriemias verdaderas (BV) o significativas en los SUH son la infección del tracto urinario (ITU) (45%) y la infección respiratoria (25%), respectivamente. En un segundo plano se sitúan la bacteriemia de foco desconocido y la infección intraabdominal (ambas en alrededor del 10% de los HC extraídos en el SUH) [5,6,12,13].

La etiología se debe a bacterias grampositivas en un 30-45%, gramnegativas en un 55-70% y anaerobios sobre el 1-3% [5,6,12-15]. Esta proporción puede cambiar, si la incidencia de HC contaminantes fuera excesiva, a favor de las grampositivas [14]. De forma global, las bacterias aisladas con mayor frecuencia de los HC obtenidos en los SUH son *Escherichia coli, Streptococcus pneumoniae y Staphylococcus aureus* [5,6,12-15].

La mortalidad a los 30 días de los pacientes con BV desde el SUH se ha cifrado entre 10-25% [12-15]. Ésta se relaciona con la gravedad de la situación clínica (existencia de sepsis-shock séptico), el tipo de foco primario (urinario, respiratorio, abdominal, sistema nervioso, desconocido) y las características de los pacientes (edad, comorbilidad, situaciones particulares, etc) [18,19].

Un dato relevante es que el 51% de las neumonías adquiridas en la comunidad (NAC) y el 36% de las ITU que se diagnostican en los SUH lo son en pacientes con ≥70 años [1,2,20,21], ya que en este subgrupo poblacional es más difícil establecer el diagnóstico, encontrar la indicación adecuada de extraer HC, se presentan con mayor gravedad clínica y las tasas de bacteriemia y mortalidad a corto y largo plazo son superiores [2,20-23].

Importancia de la sospecha y confirmación de bacteriemia en los Servicios de Urgencias Hospitalarios. Por todo ello, la sospecha y confirmación de la BV tiene un relevante significado diagnóstico, pronóstico y obliga a cambiar algunas de las decisiones más importantes a tomar de forma inmediata en el SUH. Entre otras, indicar el alta o ingreso, extraer HC y administrar el antimicrobiano adecuado y precoz [18,19,24,25].

Así, encontrar un modelo predictivo de bacteriemia útil y aplicable en todos los SUH que evite altas improcedentes e ingresos innecesarios, y sus consecuencias, se convirtió hace años en el objetivo de muchos autores [26-34] que combinan distintas variables clínicas, epidemiológicas y analíticas, entre las que se incluyen los biomarcadores de respuesta inflamatoria e infección (BMRII), ya que aumentan significativamente el poder predictivo de dichos modelos [35,36].

En este escenario clínico, en los últimos años, se ha acentuado la búsqueda de herramientas objetivas de ayuda para intentar establecer y predecir, ante la sospecha de infección grave, incluso en la primera valoración del paciente en el SUH (triaje) [37], un diagnóstico precoz, el pronóstico, la gravedad y, junto con la posible etiología bacteriana, la sospecha de bacte-

riemia (al ser estos factores claramente determinantes del pronóstico y la mortalidad de los procesos infecciosos) [2,24,37].

ESTRATEGIA DE LA REVISIÓN

La intención de esta revisión es poner de manifiesto la relevancia de las evidencias científicas publicadas en los últimos cinco años, aclarar las controversias existentes actuales y comparar la capacidad para predecir bacteriemia de los últimos modelos predictivos publicados desde el año 2017 con los ya existentes en esa fecha [26], año en el que se publicó una revisión que dejaba abierta la propuesta de seguir buscando un modelo con un rendimiento adecuado para los SUH [36] . Y así, a partir de ella, generar distintas recomendaciones que ayuden a definir el papel que pueden tener estos modelos o escalas en la mejora de la indicación de obtención de los HC [18,19], así como en la toma inmediata de otras decisiones diagnóstico-terapéuticas (administración precoz y adecuada del tratamiento antibiótico, solicitud de estudios complementarios y otras muestras microbiológicas, intensidad del soporte hemodinámico, necesidad de ingreso, etc.) [2,11,24,38].

Esta revisión se ha realizado en tres fases:

1.- Se llevó a cabo una búsqueda en las plataformas de bases de datos que los autores creyeron más relevantes (*PubMed, Web of Sciencie, Scopus y EMBASE*) empleando y combinando como palabras clave: ("infección" o "infection") y ("bacteriemia" o "bacteraemia") y ("hemocultivos" o "blood cultures") y ("biomarcadores" o "biomarkers) y ("procalcitonina" o "procalcitonin") y ("modelo predictivo" o "clinical prediction rule"). En esta fase, se utilizaron filtros para seleccionar los artículos solo de pacientes adultos (> 14 años) y aquellos relacionados con los SUH, en idiomas inglés y español y desde 2016 hasta enero de 2022.

2.- De todos los encontrados en la búsqueda inicial se escogieron, a juicio de los autores, los artículos relevantes en relación con la capacidad o utilidad de los distintos modelos o escalas predictivas de bacteriemia en los HC obtenidos en la primera atención de los pacientes en el SUH. Así, se excluyeron los artículos elaborados con pacientes de planta de hospitalización o en medicina intensiva. Se amplió la búsqueda manualmente a otros artículos que se consideraron de interés y se recuperaron algunos, por su relevancia, de la anterior revisión [36]. De esta forma, de los 1.790 artículos que se encontraron en la búsqueda (editoriales, cartas científicas, originales, originales breves, revisiones y metaanálisis), se seleccionaron 259 para su revisión inicial.

3.- En última instancia, se eligieron por unanimidad los artículos que cumplían con los objetivos e intereses de la revisión establecidos por los autores sobre los que elaboró esta revisión.

BIOMARCADORES: PAPEL COMO FACTORES PREDICTIVOS DE BACTERIEMIA

Aunque en los últimos años se han relacionado múltiples factores independientes como predictores de bacteriemia en los SUH [18,36], lo más relevantes y repetidos han sido: signos vitales [a la cabeza presión arterial sistólica (PAS) ≤100 mmHg, pero también temperatura (T^a) >38,3°C, frecuencia cardiaca (FC) y frecuencia respiratoria (FR)], comorbilidad (índice de Charlson ≥3), situación funcional, existencia de criterios de sepsis (tanto clásicos de Sepsis-2 [39] con criterios de síndrome de respuesta inflamatoria sistémica (SRIS) ≥2 como de Sepsis-3 [40] con un *quick Sepsis Related Organ Failure Assessment* (qSOFA ≥2) y analíticos (leucocitosis ≥12.000/mm^3, formas jóvenes o cayados >10% y trombopenia <150.000/mm^3) [41-43]. Junto a estos factores mencionados y de forma muy significativa en los últimos tres años se ha validado la utilidad de los BMRII para predecir bacteriemia [35,36]. Entre ellos, por sus resultados y disponibilidad en los SUH españoles, destacan la proteína C reactiva (PCR), las interleucinas (IL) 6 y 8, el lactato, la proadrenomedulina (proADM), la presepsina, el dímero D y el receptor soluble del activador del plasminógeno de tipo uroquinasa (suPAR) [35,36,44-51]. Pero, entre todos los BMRII, la procalcitonina (PCT) obtiene el mejor rendimiento predictivo sobre el resto para predecir bacteriemia y a su vez poder orientar hacia el patógeno causante de la infección, su evolución clínica (a sepsis grave y shock séptico) y la mortalidad [2,35,36,52-59]. De ahí que se han propuesto, desarrollado y validado diferentes modelos predictivos que incluyen, como una de sus variables con mayor peso, la PCT [52-59]. Además, un aspecto muy relevante hoy en día es que ya en el 89% de los SUH españoles existe disponibilidad para su uso, convirtiéndose en una herramienta útil y disponible de forma universal [60].

Procalcitonina. La PCT, es una proteína sintetizada primordialmente en la glándula tiroides y las células neuroendocrinas del pulmón, pero muchos otros tejidos pueden producir PCT en situaciones de infección bacteriana con/sin sepsis y con/sin bacteriemia. En condiciones normales su concentración es casi indetectable (<0,05 ng/ml) [35]. Sus concentraciones se relacionan con el grado de respuesta inflamatoria local y sistémica, la carga bacteriana y/o la concentración de endotoxina [35,36]. Por su cinética se considera muy adecuada para su utilización en los SUH, ya que se eleva significativamente en el torrente sanguíneo a las 2-6 horas tras el estímulo bacteriano y los valores máximos se encontrarán a las 12-36 horas, ya que tiene una semivida de alrededor de 24 horas [35].

Para ser útil, la PCT debe proporcionar información adicional a la que se obtiene con los datos clínicos del paciente con infección y ayudar a la hora de tomar decisiones urgentes en los SUH [35]. No obstante, nunca puede sustituir ni a la exploración física y anamnesis, ni a las pruebas complementarias y microbiológicas que sean pertinentes [35,36]. En el caso de la predicción de bacteriemia, debería ser capaz de identificar en el propio SUH a los pacientes con una elevada probabilidad (incluso antes de que se manifiesten los signos y síntomas de una infección bacteriana grave como hipotensión, hiperlactacidemia o disfunción de órganos) de la existencia de bacteriemia y de la etiología bacteriana del cuadro [35]. Por lo tanto, aumentará la seguridad y acortará el tiempo del diagnóstico clínico de la infección bacteriana (frente a otras causas de respuesta

inflamatoria sistémica o gravedad clínica), permitiendo el inicio del tratamiento antimicrobiano precoz y adecuado [29,39,40].

Dentro de sus reconocidas utilidades en el paciente con infección en el SUH destaca su capacidad de predecir BV concomitante, incluso con capacidad de predecir la existencia de hemocultivos contaminados [14,35]. Es conocido que existe una relación demostrada entre la mortalidad, la gravedad de situación clínica del paciente de acuerdo con los criterios de sepsis y SS, la confirmación de bacteriemia posterior y los valores de PCT en el momento de la extracción de los HC [2,5,35]. Cisneros et al [5] comunicaron que la frecuencia de bacteriemia aumentaba con la gravedad del cuadro clínico, desde el 17-31% en pacientes con criterios de sepsis y el 30-45% cuando existía SS. En otro estudio similar [61], realizado en 984 pacientes con sospecha de bacteriemia atendidos en urgencias, se obtuvieron HC positivos en el 1% de los casos cuando la PCT era <0,5 ng/ml, el 8% si la PCT era de 0,5-2 ng/ml, el 20% si >2 ng/ml y el 46% si era >10 ng/ml.

Aunque son múltiples los estudios publicados en la última década, uno de los trabajos más relevantes publicados es un metaanálisis [62] que incluye 58 estudios con 16.514 pacientes (3.420 con bacteriemia), donde el punto de corte (PC) en los distintos estudios varía de 0,1 a 17 ng/ml. Establece para todos los casos un área bajo la curva de la característica operativa del receptor (ABC-COR) de 0,79 con un PC óptimo de 0,5 ng/ml que obtiene una sensibilidad (S) del 76% (IC 95%: 72-80) y una especificidad (E) del 69% (IC 95%: 64-72). En este metaanálisis para el subgrupo de los 1.425 enfermos de los SUH los resultados fueron: ABC-COR de 0,78 con S del 76% (IC 95%: 69-82) y E del 68% (IC 95%: 61-75). Lo que confirma que la capacidad de predicción de BV con una PCT > 0,50 ng/ml, es similar o incluso mayor que la mayoría de los modelos que utilizan otras variables [35,36].

Por otro lado, y como valor añadido, algunos estudios además de predecir la existencia de BV, también han buscado las situaciones o el PC que pudiera predecir si el patógeno aislado sería gramnegativo o grampositivo. En este sentido, destaca el publicado por Thomas-Rüddel [63] sobre 4.858 pacientes, donde la PCT fue significativamente mayor en la bacteriemia por gramnegativos en comparación con la bacteriemia por grampositivos (p <0,001). El ABC-COR fue de 0,72 (IC 95%:0,71-0,74) para la predicción de bacteriemia por gramnegativos en comparación con todos los demás resultados de hemocultivos, incluidos los hemocultivos negativos. El PC optimizado fue de 10 ng/ml (S del 69%, E del 35%). La PCT difirió significativamente entre grupos específicos de patógenos (p <0,001) con concentraciones más altas en *Escherichia coli*, *Streptococcus* spp y otras enterobacterias. De la misma forma, con un ABC-COR de 0,70 y un PC >2,54 ng/ml, otro estudio determina que a mayor concentración de PCT existe mayor probabilidad de que la bacteria sea gramnegativa [64]. En esta línea, un estudio español [65] sobre 474 NAC (17,9% con BV) llegó a establecer que con una PCT ≥0,95 ng/ml se consigue una ABC para predecir bacteriemia por *S. pneumoniae* de 0,98 (IC 95%: 0,90-0,99), con un valor predictivo negativo (VPN) del 98,8%.

NUEVOS MODELOS PREDICTIVOS

Hoy en día, si bien la técnica de extracción de los HC está bien protocolizada [3,8], todavía hay importantes controversias en relación a las indicaciones de cuándo debemos obtenerlos en el SUH [2,7,8]. La obtención de HC es una práctica creciente en la valoración inicial de los pacientes con sospecha de infección en el SUH [2,15-17]. Su obtención constituye aún un motivo de discusión, ya que comparadas con el resto de pruebas habituales en urgencias, requieren un mayor tiempo para su obtención, una buena técnica para evitar contaminaciones y carecen de utilidad diagnóstica inmediata [67]. En ellos, la sospecha y confirmación de bacteriemia tiene un importante significado diagnóstico, pronóstico y terapéutico. Pero, además, los HC también se obtienen en el SUH como garantía de continuidad asistencial, ya que del conocimiento de sus resultados dependerá el manejo y evolución posterior del paciente en su destino final [2,8,15].

En los últimos años se han propuesto distintos modelos predictivos para los SUH de distinta complejidad [26-36, 52-59]. En ellos, ha adquirido una gran relevancia el papel que pueden jugar los BMRII [35,36], y en especial la PCT [35,36, 52-59], como factores predictores independientes de bacteriemia. Se ha demostrado que su capacidad pronóstica puede igualar, e incluso superar, la que consiguen distintos modelos que no la incluyen [35,36].

Hasta hace unos años, el conocido modelo predictivo de bacteriemia de Shapiro et al [26]., ha sido el más utilizado, va-

Tabla 1 | **Factores pronósticos de bacteriemia en el servicio de urgencias del modelo de Shapiro**

CRITERIOS MAYORES	Temperatura > 39,4°C (3 puntos)
	Sospecha clínica de endocarditis (3 puntos)
	Portador de catéter vascular (2 puntos)
CRITERIOS MENORES	Temperatura 38,3 – 39,3°C (1 punto)
	Edad > 65 años (1 punto)
	Tiritona (1 punto)
	Vómitos (1 punto)
	PAS < 90 mmHg (1 punto)
	Neutrofilia > 80% (1 punto)
	Leucocitos > 18.000/mm3 (1 punto)
	Porcentaje de cayados > 5% (1 punto)
	Trombopenia < 150.000 plaquetas/mm3 (1 punto)
	Creatinina > 2 mg/dl (1 punto)
RIESGO	- Alto: > 5 puntos (HC+: 15-25 %)
	- Moderado: 2-5 puntos (HC+: 7-9 %)
	- Bajo: 0-1 punto (HC+: < 1 %)

PAS: presión arterial sistólica. HC+: hemocultivos positivos. Adaptado de Shapiro et al. [26].

lidado y la referencia para los SUH en todo el mundo [27,64]. Así, Shapiro et al [26]. publicaron una propuesta de modelo que clasificaba el riesgo de bacteriemia en tres grupos de bajo (<1%), moderado (7-9%) y alto (15-26%) riesgo, en función de unos criterios mayores y de unos criterios menores (Tabla 1). Según este modelo de decisión, estaría indicada la extracción de HC cuando se cumpliera un criterio mayor o, al menos, dos menores [26]. La escala de Shapiro original publicó un ABC-COR de 0,80 en la cohorte de validación y de 0,75 en la derivación [26], con una S del 94% (IC 95%: 89%-99%) y una E del 48% (IC 95%: 42%-53%).

Otros modelos más recientes [28], aunque útiles, no consiguen alcanzar el rendimiento del modelo de Shapiro [26]. Así, un estudio multicéntrico colombiano define un modelo combinando, que incluye la $T^a \geq 38°C$, plaquetas < 150.000/mm^3 y una puntuación <15 de la escala del coma de Glasgow, con el que se obtiene un ABC-COR de "solo" 0,68 (IC 95%: 0,65-0,72) [28].

Por otra parte, como ya se ha comprobado, cuando se incluye la PCT a estos modelos se incrementa significativamente su poder predictivo. La propuesta de Tudela et al [29]., que relacionó variables clínicas, analíticas y el índice de comorbilidad de Charlson, tras el análisis de regresión, define dos variables significativas (índice de Charlson ≥ 2 y una PCT >0,4 ng/ml, 1 y 2 puntos, respectivamente) con las que se establecieron 4 grupos de probabilidad creciente de bacteriemia y con un ABC-COR de 0,80 y un VPN del 95,3% (IC 95%: 90,8-97,6) para "descartar" la existencia de bacteriemia. En otro trabajo, un grupo español [61] añadió como un "nuevo criterio mayor" a los de los de Shapiro et al [26]. el objetivar una PCT >2 ng/ml, con lo que reclasificó a los pacientes mejorando la predicción de BV en los nuevos grupos de «riesgo moderado» y «riesgo alto» (del 8,9% al 12%) y (del 16% a 24%), respectivamente.

Contenti et al [51] consiguen un ABC-COR de 0,83 similar al modelo de Shapiro, pero solo con una variable, la PCT, aunque elevando el PC de ésta a concentraciones mayores de 2,25 ng/ml. Lo que confirma lo ya dicho anteriormente que la inclusión de la PCT en cualquier modelo o como factor individual, hoy en día, debería ser considerada en los SUH como sugieren distintos autores aunque con un PC menor (0,50 ng/ml) [36].

Nuevos modelos que incluyen procalcitonina. La escala original de puntuación 5MPB-Toledo [52] incluye variables fácilmente obtenibles en el primer momento de la atención de los pacientes con sospecha de infección grave: exploratorias (T^a y FR), de comorbilidad (índice de Charlson) y analíticas (recuento de leucocitos y concentración sérica de PCT). Con el análisis de 2.181 episodios de HC extraídos, 262 de ellos con BV (12%), se construyó un sistema de puntuación de riesgo en el que se asignó una puntuación a cada variable: T^a>38,3°C (1 punto), índice de Charlson ≥3 (1 punto), FR ≥22 respiraciones por minuto (1 punto), leucocitos >12.000/mm^3 (1 punto) y una PCT ≥0,51

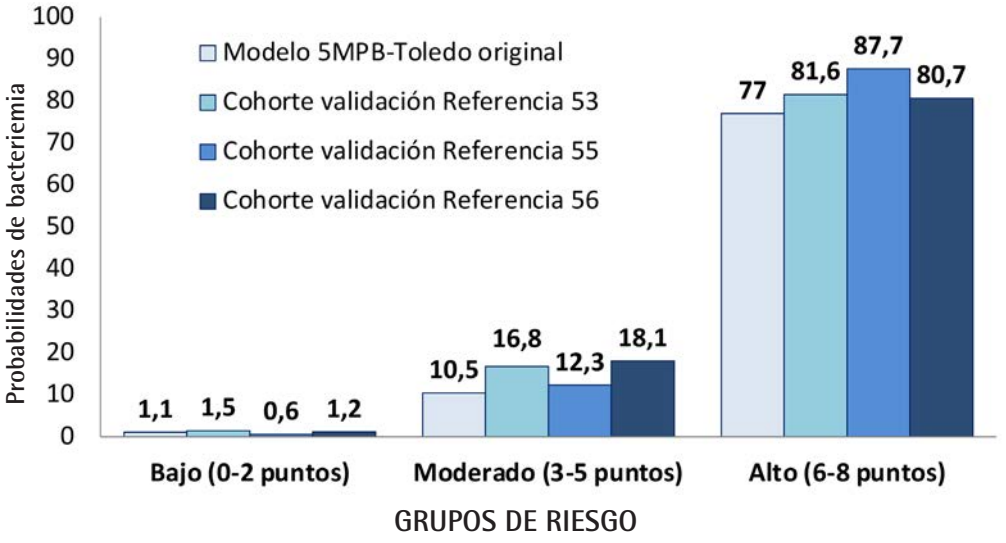

Figura 1 | **Probabilidades de bacteriemia según grupos de riesgo del modelo 5MPB-Toledo**

5MPB-Toledo: Modelo predictivo de bacteriemia de 5 variables de Toledo;
Referencia 53.- Validación del modelo predictivo de bacteriemia (5MPB-Toledo) en los pacientes atendidos en el servicio de urgencias por infección. Enferm Infecc Microbiol Clin. 2022; 40: 102-112
Referencia 55.- Utilidad del modelo 5MPB-Toledo para predecir bacteriemia en el paciente con neumonía adquirida en la comunidad en el Servicio de Urgencias. Rev Esp Quimioter 2021;34:376-382
Referencia 56.- Utilidad del modelo 5MPB-Toledo para predecir bacteriemia en el paciente anciano. Infectio. 2022; 26: 128-136

ng/ml (4 puntos) [52]. Así, se categorizó a los pacientes en tres grupos distintos de bajo (0-2 puntos), moderado (3-5 puntos) y alto (6-8 puntos) riesgo (Figura 1), con una probabilidad de bacteriemia de 1,1%, 10,5% y 77%, respectivamente. El ABC-COR del modelo fue de 0,946 (IC 95%: 0,933-0,960), rendimiento superior al de todas las escalas antes comentadas [36]. Pero lo más relevante de este modelo (5MPB-Toledo) es que ya ha sido validado en distintos trabajos multicéntricos. El primero [53] con 3.843 episodios de HC, de ellos 839 con BV (21,83%) con una probabilidad de bacteriemia de 1,5%, 16,8% y 81,6%, para los grupos de bajo, moderado y alto riesgo. El ABC-COR del modelo de validación fue de 0,932 (IC 95%: 0,924-0,940). El rendimiento diagnóstico del modelo con un PC ≥ 5 puntos consigue una S del 94,76% (IC 95%: 92,97-96,12), E del 81,56% (IC 95%: 80,11-82,92) y un VPN del 98,24% (IC 95%: 97,62-98,70). En este estudio, además, se analizaron subgrupos con especial interés para los SUH: pacientes en tratamiento con corticoides, con inmunodepresión, dados de alta desde el propio SUH o aquellos que habían recibido antibioterapia en las 72 horas previas a la extracción de los HC. Además, recientemente se han publicado otro estudio que valida el modelo para el proceso infeccioso (NAC) [55] que origina más ingresos en el servicio de Medicina Intensiva y diagnósticos de sepsis y shock sépticos en los SUH y, a la vez, es el segundo foco más frecuente de BV de los HC obtenidos en el SUH [5,6,12-15]. Finalmente, también se ha validado el modelo en los pacientes mayores de 65 años [56], subgrupo que engloba hoy en día al 35% de los pacientes que se atienden el los SUH españoles por un proceso infeccioso [1,2].

En la figura 1 se muestran la probabilidad observada de cada grupo de riesgo del modelo original y los estudios de validación del 5MPB-Toledo.

En la tabla 2 se muestra el rendimiento predictivo del modelo 5MPB-Toledo y los distintos estudios y subgrupos de validación, así como los resultados con el PC elegido como óptimo fijado ≥ 5 puntos.

Los resultados de estos estudios permiten validar externamente un modelo de riesgo sencillo para predecir bacteriemia en los pacientes adultos atendidos por un episodio de infección en los SUH. Los excelentes ABC-COR obtenidos (tabla 2) y la distribución del porcentaje de BV en cada grupo de riesgo (Figura 1) clasifican a los pacientes en 3 categorías bien diferenciadas. Por su parte, el PC ≥ 5 puntos ofrece en todos ellos una S > 90%, una E > 73% y un VPN > al 97%, lo que representa una garantía evidente para descartar la existencia de bacteriemia en un paciente con diagnóstico clínico de infección. Todo ello supone, si el juicio clínico, el tipo de proceso y las características del paciente lo permiten, que estos puedan ser dados de alta con el tratamiento antimicrobiano adecuado y optimizar la decisión de extracción de los HC en el SUH con eficacia y seguridad [2,24,36].

Recientemente, se ha publicado el modelo MPB-INFURG-SEMES [59], que aunque se ha desarrollado con otra metodología (grupos de derivación y validación), en realidad añade dos variables más al modelo 5MPB-Toledo [59]. Se trata de un estudio elaborado en 71 SUH españoles con 4.439 casos (70% en el grupo de derivación y 30% en validación) con 889 BV (20,25%). Tras el análisis de regresión logística por el método de introducción, el modelo asignó una puntuación a cada variable de forma que cada paciente podría obtener de 0 a 10 puntos: PCT ≥ 0,51 ng/ml (4 puntos); T^a>38,3°C (1 punto); índice de Charlson ≥3 (1 punto); FR ≥22 respiraciones por minuto (1 punto); leucocitos >12.000/mm^3 (1 punto); existencia de tiritona/escalofríos (1 punto) y recuento de plaquetas < 150.000/mm^3 (1 punto). El modelo consigue un excelente ABC-COR en la cohorte de derivación de 0,924 (IC 95%:0,914-0,934) y en la de validación de 0,926 (IC 95%: 0,910-0,942), superior a las publicadas anteriormente [35,36] y solo comparables a las del MPB-Toledo [52,53,55,56]. En este sentido, el MPB-INFURG-SEMES se compara por sus autores con el modelo de Shapiro en la muestra total obteniéndose un ABC-COR de 0,752 (IC 95%: 0.731-0.733) para los criterios de Shapiro (similar a la comunicada en los estudios de validación de dicho modelo) [26,27]. El PC de la escala MPB-INFURG-SEMES con mayor rendimiento conjunto e interés clínico es ≥ 5 puntos, de forma que obtiene una S del 95,94%, E de 76,28%, un VPP de 53,63% y un VPN del 98,50%. Finalmente, un dato relevante es destacado por los autores, que la mortalidad a 30 días de los pacientes con BV de su muestra fue del 16,7% frente al 8,7% cuando los hemocultivos fueron negativos [59]. Por todo ello, por la importancia para la toma de decisiones urgentes en el propio SUH y para estimar el pronóstico del paciente, los autores crearon una calculadora de la escala MPB-INFURG-SEMES (https://mpbscore.urgenciasclinico.com) para que esté disponible para cualquier clínico en los SUH (recordando que no está validada para pacientes de otros entornos como pacientes hospitalizados o de medicina intensiva, ambulatorios de atención primaria, institucionalizados en residencias, etc.). En la figura 2 se describe el riesgo de bacteriemia para cada paciente según la puntuación obtenida con el modelo MPB-INFURG-SEMES y se muestran las recomendaciones de actuación en los SUH para cada caso [59].

SITUACIONES CLÍNICAS DE ESPECIAL INTERÉS

Algunos procesos, por su importancia cuantitativa y cualitativa (ITU y NAC) o situaciones especiales (pacientes ancianos, inmunodeprimidos y neutropénicos) [35,36], donde las manifestaciones clínicas son más inespecíficas y el pronóstico más incierto y difícil, merecen algunas consideraciones especiales.

Neumonía adquirida en la Comunidad. En la actualidad (sin incluir los episodios de neumonía por la COVID-19), el 1-2% de los pacientes que se atienden en los SUH se diagnostican de NAC [4,21,66]. Su incidencia oscila entre 2-5 casos/1.000 habitantes/año [2,21]. En su atención inicial se toman HC en el 15-20% de los episodios [2,21]. La NAC es responsable de la mayoría de sepsis y shock sépticos diagnosticados en los SUH. Asimismo, representa la primera causa de muerte y de ingreso en la unidad de cuidados intensivos (UCI) (2-10%) por enfermedad infecciosa desde los SUH [2,21]. Se le atribuye una mortalidad global del 10-14% a los 30 días según la edad y

Tabla 2 **Rendimiento predictivo de bacteriemia verdadera del modelo 5MPB-Toledo original y en diferentes estudios y subgrupos, así como del punto de corte ≥ 5 puntos**

Estudio [referencia] Año publicación	n = pacientes incluidos número BV (%)	ABC-ROC (IC 95%) del modelo 5MPB-Toledo	Rendimiento del punto de corte ≥ 5			
			Sensibilidad % (IC 95%)	Especificidad % (IC 95%)	VPP % (IC 95%)	VPN % (IC 95%)
Original [52] 2020	n = 2.181 262 (12%)	0,946 (0,933-0,960)	nd	nd	nd	nd
Validación [53] 2022	n = 3.843 839 (21,83%)	0,932 (0,924-0,940)	94,76 (92,97-96,12)	81,56 (80,11-82,92)	58,93 (56,25-61,57)	98,24 (97,62-98,70)
Pacientes con antibioterapia en las 72 horas previas [53] 2022	n = 607 113 (18,56%)	0,916 (0,883-0,948)	93,00 (87,99-98,00)	90,13 (87,54-92,73)	65,00 (62,36-67,64)	98,5 (97,86-99,14)
Pacientes dados de alta desde el SUH [53] 2022	n = 813 180 (22,19%)	0,961 (0,945-0,977)	91,42 (84,87-97,98)	91,25 (89,22-93,28)	49,62 (47,00-52,24)	99,06 (98,44-99,68)
Pacientes con inmunodepresión [53] 2022	n = 541 98 (18,12%)	0,908 (0,883-0,933)	99,17 (97,56-100)	82,38 (78,73-86,02)	61,98 (59,50-64,46)	99,76 (99,58-99,94)
Pacientes en tratamiento con corticoides [53] 2022	n = 215 49 (23,16%)	0,921 (0,877-0,965)	95,91 (90,37-100)	80,93 (75,67-86,18)	53,39 (50,73-56,05)	98,88 (98,26-99,50)
Validación [55] 2021	n = 1.020 162 (15,9%)	0,915 (0,898-0,933)	97,5 (95,1-99,9)	73,2 (70,2-76,2)	40,9 (36,4-45,1)	99,4 (99,1-99,8)
Validación [56] 2022	n = 2.401 579 (24,11%)	0,908 (0,897-0,924)	94 (92-96)	77 (76-79)	57 (54-60)	97 (96-98)

ABC-ROC (IC 95%): Área bajo la curva de la caracteríostica operativa del receptor; 5MPB-Toledo: Modelo predictivo de bacteriemia de 5 variables de Toledo; BV: bacteriemia verdadera; N=número; IC: intervalo de confianza; VPP: valor predictivo positivo;

VPN: valor predictivo negativo; nd: datos no disponibles

Referencia 52.- Modelo 5MPB-Toledo para predecir bacteriemia en los pacientes atendidos por infección en el servicio de urgencias. Emergencias. 2020;32:81-9.

Referencia 53.- Validation of a predictive model for bacteraemia (MPB5-Toledo) in the patients seen in emergency departments due to infections. Enferm Infecc Microbiol Clin. 2022; 40: 102-112. doi.org/10.1016/j.eimc.2020.12.007

Referencia 55.- Utilidad del modelo 5MPB-Toledo para predecir bacteriemia en el paciente con neumonía adquirida en la comunidad en el Servicio de Urgencias. Rev Esp Quimioter 2021;34:376-382

Referencia 56.- Utilidad del modelo 5MPB-Toledo para predecir bacteriemia en el paciente anciano. Infectio 2022; 26: 128-136

factores de riesgo asociados, entre ellos la coexistencia de bacteriemia que aumenta la mortalidad hasta el 20-25% [2,5,21]. En más del 75-80% de las NAC con bacteriemia se confirma *S. pneumoniae* como el patógeno causal [65,67].

La capacidad de la PCT para predecir o descartar la existencia de bacteriemia en la NAC ha sido confirmada por distintos autores, aunque el PC adecuado continua siendo el punto más controvertido, las distintas propuestas varían considerablemente en un intervalo entre 0,10-2 ng/ml [68]. Aunque se ha estimado como válido un PC ≥ 0,51 ng/ml para predecir bacteriemia en la NAC, cuando las concentraciones de PCT son superiores a 0,95 ng/ml, la probabilidad de predecir bacteriemia por *S. pneumoniae* es mucho mayor, con un ABC-COR de 0,97 (IC 95%: 0,90-0,99), una S del 95%, una E del 91% y un VPN del 99% [36,65,67,68]. Este aspecto es relevante incluso en las NAC afebril o con hipotermia que se presentan en el SUH con BV por *S. pneumoniae* que pueden representar hasta el 4,7% y 4,3%, respectivamente, de las BV en pacientes con NAC [68,69]. Por ello, y como se ha discutido la conveniencia o no de extrae HC en todos los pacientes con NAC en el SUH por su baja rentabilidad y alto coste [70], se justifica que en aquellos pacientes con NAC y una PCT ≥ 0,51 ng/ml se extraigan HC y se elija una antibioterapia adecuada para una posible NAC bacteriémica por *S. pneumoniae* [21,68].

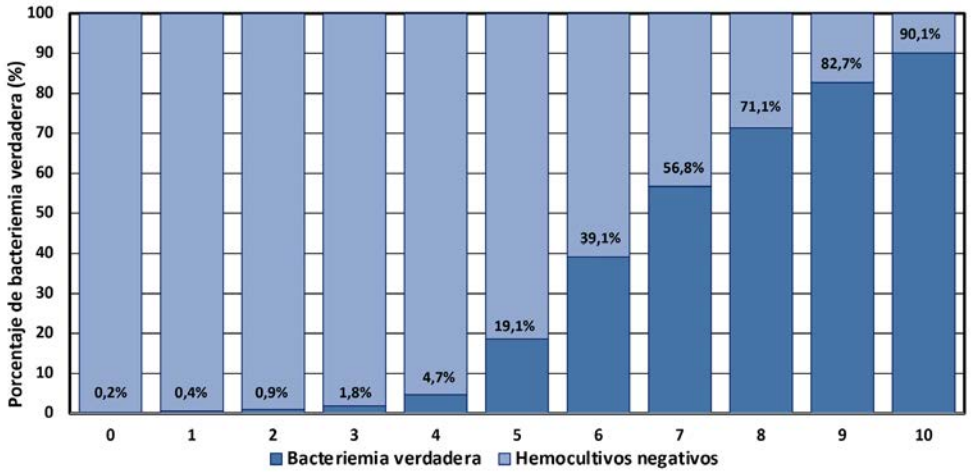

Figura 2 | **Riesgo de bacteriemia verdadera según la puntuación obtenida en el modelo MPB-INFURG-SEMES y recomendaciones de actuación en el Servicio de Urgencias Hospitalario.**

PUNTOS:

0-2 puntos: Riesgo muy bajo. Recomendación: se puede desaconsejar la obtención de hemocultivos.

3 puntos: Bajo riesgo. Recomendación: podría desaconsejarse la obtención de hemocultivos.

4 puntos: Bajo-moderado riesgo. Recomendación: la obtención de hemocultivos y la hospitalización debe valorarse individualmente.

5 puntos: Moderado-alto riesgo. Recomendación: se deben obtener hemocultivos y decidir lugar de hospitalización y antibioterapia

6-7 puntos: Alto riesgo. Recomendación: obtener hemocultivos, decidir ingreso (planta o medicina intensiva) y administrar antibióticos.

8-10 puntos: Riesgo muy alto. Recomendación: obtener hemocultivos, ingreso (planta o medicina intensiva) y administrar antibióticos.

Aunque se han publicado recientemente distintos modelos predictivos de bacteriemia en pacientes con NAC, ninguno consigue el rendimiento del MPB-Toledo [52,55] o el MPB-INFURG-SEMES [59] en estos pacientes valorados en los SUH. Así, uno de ellos de Kim et al [71]., realizado en 8 SUH clasificó a los enfermos en grupos de bajo (1,2% de BV), moderado (7,2% de BV) y alto riesgo (31,5% de BV). El ABC-COR para el modelo de bacteriemia en la cohorte de validación externa fue de 0,81, mostrando una S y E de la sensibilidad y especificidad de 68% 81%, respectivamente. En este modelo se utiliza la PCR como BMRII. Este mismo rendimiento con ABC-COR significativamente menores a las de los modelos que incluyen la PCT, ya se habían publicado y validado hace años específicamente para las NAC siendo hasta ahora referencias para este proceso infeccioso, como en el caso de los modelos de Lee et al [72] y Falgera et al [73].

Por ello, y por los resultados antes comentados, los autores creen justificado y oportuno utilizar los modelos 5MPB-Toledo [52] y el MPB-INFURG-SEMES [59] que coinciden con las recomendaciones ya efectuadas anteriormente años atrás por distintas sociedades científicas para indicar la extracción de HC en el SUH en los episodios de NAC [21,36,68].

Infección del tracto urinario. La ITU es uno de los procesos infecciosos más frecuentes atendidos en los SUH, en la actualidad alrededor del 3-4% de los pacientes que se atienden se diagnostican de este proceso [1,2,20]. En su atención se toman muestras para estudios microbiológicos en un 66% de los casos [2,20]. Entre ellos, por detrás del cultivo de orina (52,8%), predomina la obtención de hemocultivos (HC) que se realiza en el 13,7% de pacientes con el diagnóstico de ITU en el SUH, aunque su indicación es variable [2,20]. Las ITU son responsables de un relevante número de los casos de sepsis y shock sépticos diagnosticados en los SUH (solo por detrás de las infecciones respiratorias de vías bajas) [2,20]. Aunque, la mortalidad intrahospitalaria y a los 30 días de los pacientes con ITU es inferior a la mayoría de las infecciones diagnosticadas en los SUH (3-5% frente al 10-15% de forma global) [4-7]. Pero, cuando existe bacteriemia asociada a la ITU la mortalidad puede aumentar hasta 3-4 veces más que en los mismos procesos sin bacteriemia [2,5,13,20].

Clásicamente, el interés de los BMRII en las ITU en los SUH [74] se ha centrado en distinguir las infecciones no complicadas de los casos de pielonefritis agudas (PNA) y las sepsis de origen urológico. Van Nieuwkoop et al [75], en un estudio de 581 pacientes adultos, encontraron que para distinguir una ITU no complicada de una PNA con una PCT > 0,25 ng/ml se

obtenía una S del 95% (IC 95%: 0,89-0,98) y una E del 50% (IC 95%: 0,46-0,55), por lo que una PCT >0,25ng/ml debe hacer sospechar PNA, y valores >1 ng/ml bacteriemia y sepsis urológica [36,75]. En este estudio, con un PC > 0,25 ng/ml de PCT, consigue una S del 95% (IC 95%: 89%-98%) y E del 50% (IC 95%: 46%-55%) para sospechar bacteriemia [75]. No obstante, no se ha aclaró algo cuestionado desde hace años, y es a qué pacientes con ITU se les debería indicar la extracción de HC [36]. Julián et al [76], recomiendan obtener HC en los pacientes con ITU siempre que la PCT sea >1 ng/ml, ya que establecen que para un PC ≥ 1,16 ng/ml el rendimiento es muy importante con una S del 100%, una E del 97%, un VPN del 100%, y un ABC de 0,99 (IC95%: 0,98-1).

En realidad, en los últimos años se han publicado distintos modelos predictivos de BV en pacientes con ITU [77-79], pero todos ellos tienen una muestra muy limitada (menos de 400 pacientes con ITU) y unos resultados significativamente menores a los comentados anteriormente cuando se analizan los subgrupos de pacientes con ITU en los modelos 5MPB-Toledo [52] y MPB-INFURG-SEMES [59], por lo que no pueden ser recomendados de forma generalizada. Incluso alguno de ellos se ha comparado con el modelo de Shapiro obteniendo peores resultados que éste [78]. En relación a la utilidad del modelo 5MPB-Toledo en los pacientes con ITU (resultados no publicados de los autores) en una muestra de 1.499 episodios con 277 BV (18,5%) el ABC-COR del modelo fue de 0,937 (IC 95%:0,926-0,949) y el rendimiento diagnóstico del modelo con un PC ≥5 puntos consigue una S de 97,47% (IC 95%: 94,64-98,89), E de 76,68% (IC 95%: 74,18-79,00) y un VPN de 99,26% (IC 95%: 98,41-99,67). En este caso la probabilidad de BV en función del grupo de bajo (0-2 puntos), moderado (3-5 puntos) o alto (6-8 puntos) riesgo es de 1,2%, 11,1%, y 70,2%, respectivamente. Resultados en la línea del resto de estudios de validación de dicho modelo (figura 1). En este sentido, como ya se ha hecho con la NAC [24], la valoración de los enfermos con ITU en los SUH con los modelos elegidos de predicción de BV y gravedad clínica, pueden ser herramientas que optimicen las decisiones y lugar de tratamiento antimicrobiano [80].

Pacientes mayores. Un dato relevante es que el 51% NAC y el 36% de las ITU que se diagnostican en los SUH lo son en pacientes con ≥70 años [1,2,5,21], no en vano el 35% de los enfermos diagnosticados de procesos infecciosos en los SUH tienen más de 65 años. Y, es conocido, que en este subgrupo poblacional es más difícil establecer el diagnóstico, encontrar la indicación adecuada de extraer HC, se presentan con mayor gravedad clínica y las tasas de bacteriemia y mortalidad a corto y largo plazo son superiores [2,21].

En relación con este subgrupo etario, recientemente se han publicado pocos estudios, por lo que los clásicos siguen siendo la referencia [23,36,81,82]. Por ello, en este caso nos remitimos a los resultados del estudio de validación de los nuevos modelos [56]. En él se incluyeron 2.401 pacientes. De ellos, se consideró como BV a 579 (24,11%). Los resultados del riesgo de BV según la categorización de los grupos y el rendimiento del PC ≥ 5 puntos de la escala 5MPB-Toledo se pueden consultar en la tabla 2 y la figura 1. Según estos, en la actualidad, los autores también recomiendan estas escalas con PCT para valorar el riesgo de BV en los pacientes con sospecha de infección bacteriemia en los SUH.

PREVISIONES DE FUTURO

Aunque aún no son habituales en los SUH, se han publicado modelos de predicción a través de redes neuronales artificiales combinando varios BMRII como son la PCT, IL-6, lactato y dímero D. Aún así, son estudios con poca muestra y que consiguen un rendimiento prometedor (sensibilidad de 82% y especificidad de 85%) en los que la PCT con un PC > 2 ng/ml, es el factor que más peso aporta al método [83]. En este sentido, Choi et al [84], recientemente han publicado un estudio en el que desarrollan varios modelos de predicción con calculadoras que utilizan variables conseguidas en el triaje inicial del paciente (datos demográficos, signos vitales, nivel de triaje y analíticos urgentes) y que consiguen desde un ABC de 0,718 hasta un ABC de 0,853, superior a otros modelos pero no de forma significativa .

Otro trabajo recientemente publicado de Lee et al [85] usando inteligencia artificial y con una muestra retrospectiva de 622.771 hemocultivos y 38.752 BV consigue un ABC-COR de datos de 12 y 24 horas de 0,762 (IC 95%: 0,7617-0,7623) y 0,753 (IC 95%: 0,752-0,753), respectivamente.

Otra línea de estudio la aporta una propuesta de árboles de decisión donde se selecciona los pacientes (según la existencia de SRIS ≥2, qSOFA≥ 2, criterios de Shapiro o el MEDS) del grupo definido de alto riesgo de bacteriemia para realizar de forma urgente técnicas de detección rápida [86,87], el problema de estos modelos es que aunque consiguen una alta S, la E es muy baja, por lo que, de momento, no pueden ser recomendados de forma rutinaria.

En un futuro muy cercano, en la atención al paciente con infección grave en los SUH, en el propio triaje se dispondrá de escalas o modelos automáticos o electrónicos que seleccionarán a los pacientes con alta probabilidad de infección bacteriana, a los que se les aplicará los modelos predictivos de bacteriemia y gravedad-mortalidad, de forma que se pueda optimizar el diagnóstico microbiológico (indicación de obtener HC) y las medidas terapéuticas (antibioterapia adecuada y precoz, control del foco) [2,88,89].

CONCLUSIONES Y RECOMENDACIONES

A partir de la evidencia acumulada sobre todo lo comentado de la capacidad de los nuevos modelos predictivos de bacteriemia con disponibilidad para ser evaluados, hoy en día, en los SUH, podemos decir que tanto el 5MPB-Toledo como el MPB-INFURG-SEMES representan herramientas útiles para la estratificación del riesgo real de BV en los pacientes atendidos en los SUH por los distintos procesos infecciosos que se valoran en dichos dispositivos. Ambos, son capaces de predecirla con variables fácilmente obtenibles en la primera valoración

del paciente con sospecha o confirmación de padecer una infección. Pero, siempre, junto al juicio clínico y otras variables independientes del proceso y del paciente. De esta forma, facilitan la toma de decisión de indicación de obtención de HC y la estrategia diagnóstico-terapéutica. Además, se ha comprobado que consiguen un mayor rendimiento que el clásico modelo de Shapiro et al [26], hasta ahora la mayor referencia y más utilizado en los SUH [35,36].

FINANCIACION

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CONFLICTO DE INTERESES

- AJJ ha participado en reuniones científicas organizadas por Bayer, Boehringer, Esteve, GSK, Lilly, MSD, Pfizer, Tedec Meiji, Roche, Thermo Fisher Scientific, B.R.A.H.M.S. AG, ViroGates y Biomerieux.

- JGC ha participado en reuniones científicas organizadas por Bayer, Boehringer, GSK, MSD, Pfizer, Tedec Meiji, Thermo Fisher Scientific, Laboratorios Rubio, Rovi, LeoPharma, Sanofi, Bristol Myers Squibb, AstraZeneca, Novo Nordisk y Angelini.

- FJC ha participado en reuniones organizadas por MSD, Pfizer, Astellas, Gilead, Novartis, Astra-Zeneca, Tedec Meiji, Angelini, Bayer, GSK y ERN.

- RRD declara la no existencia de conflictos de intereses.

Ningún autor ha recibido compensación económica por participar en este trabajo.

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Review

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Interactions listed in the Paxlovid fact sheet, classified according to risks, pharmacological groups, and consequences

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ABSTRACT

Paxlovid (nirmatrelvir plus ritonavir) is a new oral antiviral therapeutic for the treatment of COVID-19. Nirmatrelvir is an inhibitor of SARS-CoV-2 main protease, while ritonavir is used as a CYP3A inhibitor in low doses to slow the metabolism of nirmatrelvir, thus enhancing their therapeutic effect. The isoenzyme CYP3A4 is responsible for at least part of the oxidative metabolism of approximately 60% of available medications and ritonavir is therefore a significant source of drug interactions. We describe here the drugs that are contraindicated or should be used with or without precautions when Paxlovid (nirmaltrevir plus ritonavir) should be administered according to each fact sheet in force at the Spanish Agency for Medicines and Health Products.

Keywords: Paxlovid, Nirmatrelvir / ritonavir, Drug interactions, COVID-19, SARS-CoV-2

Interacciones recogidas en la ficha técnica de Paxlovid, clasificadas según los riesgos, grupos farmacológicos y consecuencias

RESUMEN

Paxlovid (nirmatrelvir más ritonavir) es un nuevo tratamiento antivírico oral para la COVID-19. Nirmatrelvir es un inhibidor de la principal proteasa del SARS-CoV-2, mientras que ritonavir es usado como un inhibidor de la CYP3A a baja dosis para reducir el metabolismo de nirmatrelvir, potenciando así su efecto terapéutico. La isoenzima CYP3A4 es responsable de al menos una parte del metabolismo oxidativo de aproximadamente el 60% de los medicamentos disponibles, por lo que el ritonavir es una fuente importante de interacciones farmacológicas. Describimos los fármacos cuyo uso está contraindicado o deben utilizarse con precauciones o sin ella cuando debe administrase Paxlovid (nirmaltrevir más ritonavir), de acuerdo con cada ficha técnica vigente en la Agencia Española de Medicamentos y Productos Sanitarios

Palabras clave: Paxlovid, Nirmatrelvir / ritonavir, Interacciones medicamentosas, COVID-19, SARS-CoV-2

INTRODUCTION

The following table describes the drugs that are contraindicated or should be used with or without precautions when Paxlovid (nirmatrelvir plus ritonavir) should be administered. The information has been compiled directly from each Fact Sheet (FS) in force at the Spanish Agency for Medicines and Health Products.

The table (Table 1) has been constructed as follows:

- In the rows the drugs have been grouped using the ATC classification (Anatomical Therapeutic Chemical classification).

- The first column corresponds to the pharmacological group

- The second column, titled Fact Sheet, gathers the contraindications and use with precautions that are included in the Paxlovid FS.

- The third column, entitled alternatives, includes drugs whose use is possible with or without precautions, in patients treated with Paxlovid, as alternatives to those mentioned in the antiviral FS

- To reduce the final size of the text, a system of coding the type of interaction, its consequences and the action guideline has been used (see below).

As a general principle this document is intended as an aid to the management of Paxlovid in relation to the drugs that

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Table 1 **Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered**

	Paxlovid fact sheet	Alternatives
Gastrointestinal motility agents	**Contraindication:** cisapride (1)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal **Use with caution:** metoclopramide (1)
Anticoagulants	**Contraindication:** rivaroxaban (1), vorapaxar (1) **Use with caution:** warfarin (2), acenocumarol (2)	**Use with caution:** dabigatran (5), edoxaban (5) **Likely safe use:** heparin (6)
Antianginal	**Contraindication:** ranolazine (1)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal
Antiarrhythmics	**Contraindication:** amiodarone (1), bepridil (1)(4), dronedarone (1), encainide (4), flecainide (4), propafenone (4), quinidine (1)(4) **Use with caution:** digoxin (5)	**Use with caution:** disopyramide (4)
Calcium channel antagonists	**Use with caution:** amlodipine (1), diltiazem (1), nifedipine (1)	**Use with caution:** verapamil (1)
Endothelin antagonists	**Contraindication:** riociguat (1) **Use with caution:** bosentan (1)	**Use with caution:** ambrisentan (2)
HMG Co-A reductase inhibitors	**Contraindication:** simvastatin (1), lovastatin (1) **Use with caution:** atorvastatin (1), rosuvastatin (5)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal **Use without caution:** pravastatin (6), fluvastatin (6). pitavastatin (2)
Lipid-modifying agents	**Contraindication:** Lomitapide (1)	It should be assessed whether provisional suspension can be carried out during the 5 days of treatment with Paxlovid, and it can be restarted within 24 hours of withdrawal, continuing with the previous dose
Phosphodiesterase type 5 inhibitors	**Contraindication:** avanafil (1), sildenafil (1) (in pulmonary arterial hypertension patients), vardenafil (1) **Use with caution:** sildenafil (1) (not to exceed 25 mg/day), tadalafil (1) (not to exceed 10 mg every 72 hours)	
Alfa1-adrenoreceptor antagonist	**Contraindication:** alfuzosin (1)	**Use without caution:** terazosin (6)
Hormonal contraceptives	**Use with caution:** ethinyl estradiol (2) (barrier methods of contraception should be considered)	
Steroids	**Use with caution:** inhaled, injectable or intranasal fluticasone propionate (1), budesonide (1) and triamcinolone (1) (a glucocorticoid dose reduction should be considered), dexamethasone (1), prednisolone (1) (monitor therapeutic and adverse effects)	**Use with caution:** prednisone (1), deflazacort (1), methylprednisone (1), betamethasone (1), beclomethasone (1)
Thyroid hormone replacement therapy	**Use with caution:** levothyroxine (2)	
Antibiotics	**Contraindication:** fusidic acid (1), rifampicin (3) **Use with caution:** rifabutin (1) (reduce dose to 150 mg 3 times per week), erythromycin (1) (monitor therapeutic and adverse effects), clarithromycin (1) (avoid doses higher than 1 g per day and consider a dose reduction of 50% and 75% in patients with ClCr 30-60 and < 30 ml/min, respectively).	**Use with caution:** azithromycin (5), ciprofloxacin (2), moxifloxacin (2), tigecycline (5). **Use without caution:** b-lactams (6), aminoglycosides (6), glycopeptides (6), polypeptides (6), lipopeptides (6), oxazolidinones (6), cotrimoxazole (6), doxycycline (6), levofloxacin (6)

Table 1 **Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered (cont.)**

	Paxlovid fact sheet	Alternatives
Anti-tuberculous drugs	**Use with caution:** bedaquiline (1) (concomitant administration should be avoided. If the benefit outweighs the risk, concomitant administration of bedaquiline with ritonavir should be undertaken with caution. Monitor ECG and transaminases frequently), delamanid (1) (due to the risk of QTc interval prolongation associated with DM-6705, ECG monitoring is recommended)	**Use with caution:** rifabutin (1)(3). **Use without caution:** capreomycin (6), ethambutol (6). isoniazid (6), pyrazinamide (6)
Anti-malarial drugs	**Use with caution:** atovaquone (2)	**Use without caution:** cotrimoxazole (6)
Antifungal	**Contraindication:** voriconazole (1) **Use with caution:** ketoconazole (1) (a dose reduction should be considered), itraconazole (1) (monitor therapeutic and adverse effects)	**Use with caution:** posaconazole (5) (monitoring for adverse effects), isavuconazole (1) (monitoring for adverse effects) Use without caution: echinocandins (6), amphotericin B (6).
Antiretroviral	**Use with caution:** efavirenz (1)(2) (monitoring tolerability), maraviroc (1) (in adult patients with a creatinine clearance of <80 ml/min, the dose should be adjusted to 150 mg, once daily)	**Use with caution:** dolutegravir (2), ritonavir-boosted protease inhibitors (1) (monitoring for adverse effects) Use without caution: abacavir (6), emtricitabine (6), enfuvirtide (6), lamivudine (6), raltegravir (6), tenofovir (6), zidovudine (6)
Anti-hepatitis C virus agents	**Contraindication:** glecaprevir/ pibrentasvir (1)	**Use with caution:** ritonavir-boosted protease inhibitors (1) (monitoring for adverse effects), sofosbuvir (5), ledipasvir (5), velpatasvir (5) **Use without caution:** ribavirin (6)
Anticancer drugs	**Contraindication:** apalutamide (1)(3), dasatinib (1), nilotinib (1), vincristine (1), vinblastine (1), and neratinib (1) **Use with caution:** afatinib (5) (monitoring adverse reactions), abemaciclib (1) (adjust the dose to 100 mg twice a day), ceritinib (1) (5) (reduce the dose by 30%), venetoclax (1) (for patients who have completed the escalation phase and are receiving a constant daily dose, reduce the dose by at least 75%.), encorafenib (1) (concomitant administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk, patients should be closely monitored), fostamatinib (1) (concomitant administration of fostamatinib with ritonavir may increase exposure to the fostamatinib metabolite R406, leading to adverse events. Dose reduction may be necessary), ibrutinib (1) (reduce ibrutinib dose to 140 mg and monitor patient closely for toxicity)	**Use with caution:** acalabrutinib (1) (avoid or discontinue the drug on the fifth day of treatment with Paxlovid), alectinib (1), alitretinoin (1) (reduce the dose to 10 mg), alpelisib (2)(7), anagrelide (2), bendamustine (2), bexarotene (1), binimetinib (2), everolimus (1), bleomycin (8), bortezomib (1) (monitor adverse effects), brigatinib (1) (avoiding or reducing the dose by about 50 %, i.e. from 180 mg to 90 mg or from 90 mg to 60 mg), busulfan (1), cabozantinib (1), ceritinib (1) (reduce the dose of ceritinib by about one third, rounded to the nearest multiple of the 150 mg dose), cyclophosphamide (1) (monitoring effectiveness), dabrafenib (1)(2), dacarbazine (2), dacomitinib (1), docetaxel (1), trabectedin (avoid or reduce the dose), entrectinib (1) (avoid or reduce the dose), epirubicin (2), erlotinib (1), estramustine (8), etoposide (1), ibrutinib (1) (discontinue Paxlovid 5 days into treatment or reduce the dose to 140 mg/day), idelalisib (1) (monitoring for adverse effects), imatinib (1), idarubicin (2), ixazomib (8), lorlatinib (1) (reduce the dose), midostaurin (1), mitomycin (8), mitotane (3), mitoxantrone (5), nintedanib (5), olaparib (1) (reduce the dose to 100 mg every 12 h), paclitaxel (2), panobinostat (1) (reduce the dose), pegasparaginase (8), ponatinib (1) (reduce the dose to 30 mg/day), rucaparib (1), ruxolitinib (1) (reduce the dose by 50%), selumetinib (2), sonidegib (1) (reduce the dose to 200 mg/48 h), talazoparib (1) (avoid or reduce the dose), thiotepa (1), tivozanib (7) (separate the administration of Paxlovid by at least 2 hours), trametinib (5), tretinoina (1) (reduce the dose), tucatinib (2), vemurafenib (3), zanubrutinib (1) (reduce the dose to 80 mg/day, all 5 days during the use of Paxlovid) **Use without caution:** aflibercept (6), azacytidine (6), capecitabine (6), carboplatin (6), carfilzomib (6) cisplatin (6). cytarabine (6), cladribine (6), clofarabine (6), chlorambucil (6), decitabine (6), eribulin (6), fludarabine (6), fluorouracil (6), gemcitabine (6), lenvatinib (6), melphalan (6), mercaptopurine (6), methotrexate (6), nelarabine (6), niraparib (6), osimertinib (6), oxaliplatin (6), padeliporfin (6), pemetrexed (6), pentostatin (6), raltitrexed (6), sorafenib (6), tegafur (6). thioguanine (6), arsenic trioxide (6), vandetanib (6), vismodegib (6)

Table 1 **Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered (cont.)**

	Paxlovid fact sheet	Alternatives
Immunosuppressants	**Use with caution:** cyclosporine (1), tacrolimus (1), everolimus (1) (close monitoring of therapeutic and adverse effects)	**Use with caution:** baricitinib (5), filgotinib (8), fingolimod (1), lenalidomide (2), leflunomide (1), mycophenolate (2), pomalidomide (2), siponimod (2), teriflunomide (2), tofacitinib (1), upadacitinib (1) **Use without caution:** apremilast (6), azathioprine (6), dimethyl fumarate (6), thalidomide (6)
Analgesics	**Contraindication:** piroxicam (1)	**Use with caution:** enzymes involved in NSAID metabolism can be induced (2)
Anti-gouts	**Contraindication:** colchicine (1)	
Opioids	**Contraindication:** pethidine (1), propoxyphene (1). **Use with caution:** fentanyl (1) (monitor therapeutic and adverse effects), methadone (2), morphine (2)(dose may need to be increased)	**Use with caution:** alfentanil (1), hydromorphone (2), oxycodone (1), tramadol (1), tapentadol (2) **Use without caution:** buprenorphine (6), remifentanil (6)
Anticonvulsants	**Contraindication:** carbamazepine (3), phenobarbital (3), phenytoin (3) **Use with caution:** divalproex (2), lamotrigine (2) (close monitoring of plasma levels), phenytoin (2) (close monitoring of serum levels or therapeutic effects. May decrease serum ritonavir levels)	**Use with caution:** clonazepam (1), eslicarbazepine (2), stiripentol (1), ethosuximide (1), lacosamide (1), lamotrigine (2), oxcarbazepine (2), perampanel (1), rufinamide (3), topiramate (2), valproic acid (2) **Use without caution:** gabapentin (6), brivaracetam (6), levetiracetam (6), pregabalin (6), tiagabine (6), zonisamide (6)
Antidepressants	**Use with caution:** amitriptyline (4), fluoxetine (4), imipramine (4), nortriptyline (4), paroxetine (4), sertraline (4) (close monitoring of therapeutic effects), desipramine (1) (reduce the dose)	**Use with caution:** agomelatine (2), fluvoxamine (2), escitalopram (2), desvenlafaxine (2), duloxetine (2), maprotiline (4), mianserin (1), mirtazapine (1), moclobemide (4), reboxetine (1), trazodone (1), venlafaxine (1), vortioxetine (4)
Antipsychotics	**Contraindication:** clozapine (1), pimozide (1), lurasidone (1), quetiapine (1) **Use with caution:** haloperidol (4), risperidone (4), thioridazine (4) (monitoring therapeutic effects)	**Use with caution:** aripiprazole (1), asenapine (2), chlorpromazine (2), clotiapine (1), olanzapine (2), paliperidone (2), ziprasidone (2), zuclopenthixol (1) **Use without caution:** amisulpride (6), loxapine (6), sulpiride (6), tiapride (6)
Ergot derivatives	**Contraindication:** dihydroergotamine (1), ergonovine (1), ergotamine (1), methylergonovine (1)	
Sedative / hypnotics	**Contraindication:** clorazepate (1), diazepam (1), estazolam (1), flurazepam (1), oral midazolam (1), triazolam (1). **Use with caution:** midazolam (parenterally) (1), alprazolam (1) (precautions during the first days), buspirone (1), zolpidem (1) (monitoring hypersedation)	**Use with caution:** bromazepam (2), brotizolam (1), flunitrazepam (2), lorazepam (2), lormetazepam (2), zopiclone(1), hydroxyzine (1)
Smoke cessation	**Use with caution:** bupropion (2) (it is possible that the interaction is of no clinical significance)	
Antiasthmatic	**Use with caution:** theophylline (2)	**Use with caution:** montelukast (2), roflumilast (2)
β2-agonists	**Contraindication:** salmeterol (1)	**Use with caution:** indacaterol (1), formoterol (2), vilanterol (1) **Use without caution:** olodaterol (6), salbutamol (6), terbutaline (6)
Inhaled steroids	**Use with caution:** fluticasone propionate inhaled, injectable or intranasal (1), budesonide (1), triamcinolone (1)	**Use with caution:** beclomethasone (1), mometasone (1), ciclesonide (1)
Antihistamines	**Contraindication:** astemizole (1), terfenadine (1), fexofenadine (1) **Use with caution:** loratadine (1) (monitor therapeutic and adverse effects)	**Use with caution:** ebastine (1) **Use without caution:** cetirizine (6), levocetirizine (6), desloratadine (6)
Amphetamine derivatives	**Use with caution:** amphetamine (4) (monitoring of adverse effects)	
Herbal products	**Contraindication:** St. John's wort (Hypericum perforatum) (3)	

the treated patient may be receiving. These are global recommendations for which in many cases there is no direct confirmation of the existence and severity of the interaction other than the FS of each drug. Therefore, in no case is it a tool that replaces the responsibility of the prescribing physician.

Codes

1: Potential risk of increased substrate concentrations with risk of toxicity due to CYP3A4 inhibition. Avoid, reduce dose or monitor for adverse effects.

2: Potential risk of reduced substrate concentrations with risk of inefficacy due to Paxlovid induction. Monitor efficacy.

3: Potential risk of reduced Paxlovid concentrations with risk of reduced efficacy. Avoid.

4: Potential risk of increased substrate concentrations with risk of toxicity due to CYP2D6 inhibition. Reduce dose or monitor for adverse effects.

5: Potential risk of increased substrate concentrations due to inhibition of P-glycoprotein (P-GI) and/or breast cancer resistance protein (BCRP) produced by Paxlovid. Reduce dose or monitor for adverse effects.

6. In principle, the risk of interactions considering the profile of the drug and Paxlovid is probably very low. In any case, the combination of should be performed considering the general precautions of any combination.

7. Risk of increased Paxlovid concentrations due to increased absorption from reduced first pass in the gut. Precautions.

8. No information on the risk of interactions is available.

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CONFLICT OF INTEREST

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Optimized identification of microorganisms directly from positive blood cultures by MALDI-TOF to improve antimicrobial treatment

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ABSTRACT

Introduction. Bacteriemia is a major cause of morbidity and mortality among hospitalized patients worldwide. Early identification of microorganisms from blood culture can lead to improvement of treatment and outcomes.

Methods. The study was divided into two phases. The first phase when a comparison of the methods was made to check the concordance between them, using as a reference the standard method implemented in the laboratory. In a second phase, both methods are combined. We used the rapid identification method and when it could not identify we used the standard method. The microorganisms that were not identified by either of the two methods were identified from colony at 24 hours

Results. A total of 589 microbial positive blood cultures have been included in the present study. With the rapid method we obtained 96% and 88% identification results for Gram-negative bacilli (GNB) and Gram-positive cocci (GPC) respectively. In this study we observed that the combination of the rapid and standard method achieved identifications of 98% and 97% for GNB and GPC respectively.

Conclusions. The data analysed shows that both methods combined perform better than individually. We achieved an optimization of the identification of microorganisms directly from positive blood cultures by MALDI-TOF. This combination identified 98% of the microorganisms in between ten minutes to one hour and a half since the blood culture flagged positive.

Keywords: Maldi biotyper; Antimicrobial treatment; Direct identification; Combination of methods; Blood cultures.

Optimización en el proceso de identificación directamente de hemocultivos positivos por MALDI-TOF para mejorar el tratamiento antimicrobiano

RESUMEN

Introducción. La bacteriemia es una de las principales causas de morbilidad y mortalidad entre los pacientes hospitalizados de todo el mundo. La identificación temprana de los microorganismos que están en la sangre, permite optimizar los tratamientos y conseguir mejores resultados.

Material y métodos. El estudio se dividió en dos fases. En la primera fase se realizó una comparación de los dos métodos para comprobar la concordancia entre ambos, tomando como referencia el método estándar implementado en el laboratorio. La segunda fase combinó ambos métodos para la identificación de hemocultivos positivos. Se utilizó el método de identificación rápida como primera opción y el método estándar solo cuando no se consiguió identificar por la primera opción. Los microorganismos que no fueron identificados por ninguno de los dos métodos, se identificaron directamente de la colonia crecida a las 24 horas.

Resultados. Se analizaron un total de 589 hemocultivos positivos en este estudio. Con el método rápido obtuvimos un 96% y 88% de identificación de bacilos gramnegativos y cocos grampositivos respectivamente. En este estudio observamos que la combinación del método rápido y el método estándar consiguió identificaciones del 98% y 97% para bacilos gramnegativos y cocos grampositivos respectivamente.

Conclusiones. Los datos analizados muestran que ambos métodos combinados consiguen mejores resultados que utilizados de forma individual. Logramos una optimización de la identificación de microorganismos directamente a partir de hemocultivos positivos por MALDI-TOF. Con esta combinación se identificó el 98% de los microorganismos entre los primeros 10 minutos y hora y media de hemocultivo positivo.

Palabras clave: tipado Maldi-tof; Tratamiento antimicrobiano; Identificación directa; Combinación de métodos; Hemocultivos.

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INTRODUCTION

Bloodstream infections are a major cause of morbidity and mortality. The possibility of speeding up the identification and results of antimicrobial efficacy on bacteria grown in blood cultures and, the consequent adjustment of the appropriate antibiotic therapy is of paramount importance in patients with sepsis to improve their outcome [1,2].

Presence of microorganisms in bloodstream is a life-threatening situation that requires quick identification and treatment. Pathogen identification is of great importance, enabling adjustment of antibiotic care [3]. In most clinical microbiology laboratories, the traditional method for microbial identification includes sampling of an aliquot from the positive blood culture, subculturing it into solid agars for 18–24 h, and bacterial identification according to biochemical features and antimicrobial efficacy testing. The primary disadvantage of this method is that causative pathogen identification is performed only after colony growth and isolation, which leads to a higher turnaround time [4].

In recent years, direct identification from positive blood cultures has demonstrated reliability and a quicker comparison than MS identification from plate colonies. These methodology has shown over the eighty percent of success in colony's identification in gram negative bacilli and over the sixty five percent in gram positive cocci [5].

These methods also provide quicker turnarounds and combined with molecular and blood culture direct sensibility methods, they can provide a correct identification and measure sensibility to some antimicrobial agents within hours [6-8].

Our objective is to evaluate if the consecutive performance of two direct blood cultures identification methods is more efficient (percentage of direct positive blood cultures identifications) than the use of both methods individually.

MATERIAL AND METHODS

This study was conducted in University Hospital of La Paz in Madrid (Spain), a 1300-bed tertiary academic center that is a key part of the Spanish National Health Service, which supports a mixed urban and peri urban population of approximately 600,000 people nearby Madrid, Spain, with approximately 48,000 hospital admissions/year. Five hundred and eighty-two (582) consecutive positive blood cultures have been included in the present study.

All aerobic, anaerobic and pediatric/aerobic blood culture bottles have been incubated in a BD BACTEC™ FX automated device (Beckton Dickinson, Madrid, Spain) for up to 5 days at 37 °C until they were identified as positive. Samples were evaluated with the Bruker MALDI-biotyper system of Bruker DaltoniK (Bruker Daltonik GmbH, Bremen, Germany). Mass spectra was obtained using a Microflex LT Mass spectrometer (Bruker Daltonik GmbH) and Flex Control software. Bacterial identification was obtained using the MALDI eBiotyper 2.0 software (Bruker Daltonik GmbH). The spectra was calibrated by using *Escherichia coli* ribosomal proteins (Bruker Daltonik GmbH).

We carried out the study over a period of five months (from March 2019 to July 2019) and we divided it into two phases. On the first phase (March 2019 to May 2019), we used for identification a direct blood culture a standard method witch published in the literature [9]. In this first phase we assessed reliability and accuracy in our laboratory of an in-house 10-minute protocol for direct identification method previously validated [10]. We evaluated in parallel this faster and more economic method against our direct blood identification method [9]. On the second stage, we performed consecutively this quick method followed, in the cases in which the identification was not reliable, by the direct blood identification method implemented in our laboratory. Direct identifications have been performed during the routine schedule, so we included in our study every blood culture that tested positive during the morning shift (from 8:00 am to 15:00 pm) and we included one or more blood culture per patient in the study.

The protocols for sample processing used in both methods were followed step by step as they are published [9,10]. A brief description of these methods is following:

Rapid method added 200 µl of blood culture broth to a 1-ml solution of Triton X-100 (Sigma-Aldrich, Lyon, France) at a concentration of 0.1%. The mix was vortexed for 5 second and then centrifuged at 13,000 rpm for 2 min. The supernatant was discarded, and then a further 1 ml of 0.1% Triton X-100 was added before a second cycle of vortexing and centrifugation. The supernatant was removed again and added 20 µl of formic acid to the pellet. We changed this step respect to the original protocol because we found out that the identification was better incorporating 20 µl of acid formic than incorporating only 1,2 µl of acid formic. This mix was centrifuged at 13,000 rpm for 1 min. The supernatant was ready for identification using MALDI-TOF MS.

Standard method centrifuged 4 ml of blood culture at 800 rpm for 5 min. Then the supernatant was centrifuged at 10,000 rpm for 10 min. The pellet was washed once with 1 ml of deionized water. Then, an ethanol/formic acid extraction procedure was applied: the pellet was resuspended in 300 ml of water. 900 ml of absolute ethanol was added and the mixture was centrifuged at 13000 rpm for 2 min. The supernatant was discarded, 20 ml of formic acid (70% v/v) was added to the pellet and mixed thoroughly, 20 ml acetonitrile was added and mixed again. The mixture was centrifuged again at 13000 rpm for 1 min. One microliter of the supernatant was placed onto a spot of the steel target plate (Bruker Daltonik GmbH, Bremen, Germany) and gently mixed with 1 ml of a-cyano-4-hydroxy-cinnamic acid matrix solution in organic solvent (50% acetonitrile and 2.5% trifluoroacetic acid) and air dried at room temperature.

Identification between both methods has been considered reliable and concordant when bacterial identification was the same and the direct bacterial log (score) cut-offs ranged from 1.5 to 2.5. This range was evaluated by Simon et al [10]. They found the lower confidence score that provided the higher percentage of direct identifications without loss off accuracy.

Table 1 Distribution of identifications during phase one

Microorganisms	Total number of isolates	Correct identification by both methods	Only identification by rapid method (Simon et al) [10]	Only identification by standard method (Romero-Gómez et al) [9]	Identification by grown colony
Abiotrophia defectiva	3	3			
Bacillus cereus	1	1			
Bacillus licheniformis	1	1			
Bacteroides fragilis	2	2			
Brevibacillus parabrevis	1	1			
Candida albicans	4	2		2	
Candida lusitaniea	3	2			1
Candida parapsilosis	1	1			
Candida tropicalis	3	2	1		
Capnoctyophaga sputigena	1	1			
Citrobacter sp	1	1			
Corynebacterium afermentans	1	1			
Cutibacterium acnes	1	1			
Enterobacter cloacae	2	2			
Enterobacter kobeil	1	1			
Enterococcus casseliflavus	1	0	1		
Enterococcus faecalis	17	16		1	
Enterococcus faecium	3	3			
Escherichia coli	74	72		2	
Gemella haemolysans	1	1			
Hafnia alvei	1	1			
Klebsiella aerogenes	1	1			
Klebsiella oxytoca	7	6		1	
Klebsiella pneumoniae	14	14			
Kodamaea ohmeri	1	1			
Listeria innocua	2	2			
Listeria sp	1	1			
Micrococcus luteus	2	2			
Moraxella catarrhalis	1	1			
Moraxella nonliquefaciens	2	0	2		
Morganella morganiil	1	1			
Proteus mirabilis	1	1			
Pseudomonas aeruginosa	12	12			
Pseudomonas putida	1	1			
Rothia dentocariosa	1	1			
Rpthia mucilaginosa	1	1			
Salmonella sp	4	3		1	
Serratia liquefaciens	3	3			
Serratia marcescens	6	6			
Staphylococcus aureus	25	18	6		1
Staphylococcus capitis	7	5	2		
Staphylococcus caprae	2	2			
Staphylococcus epidermidis	84	66	7	7	4
Staphylococcus haemolyticus	12	9		1	2
Staphylococcus hominis	23	19	2		2
Staphylococcus pettenkoferi	2	2			

Table 1 Distribution of identifications during phase one (cont.)

Microorganisms	Total number of isolates	Correct identification by both methods	Only identification by rapid method (Simon et al) [10]	Only identification by standard method (Romero-Gómez et al) [9]	Identification by grown colony
Staphylococcus pseudointermedius	1	0	1		
Staphylococcus schleiferi	1	1			
Staphylococcus warneri	1	1			
Stenotrophomonas maltophilia	2	2			
Streptococcus alactolyticus	1	0	1		
Streptococcus anginosus	4	2		2	
Streptococcus dysgalactiae	5	3		2	
Streptococcus gallolyticus	1	0		1	
Streptococcus gordonii	2	0		2	
Streptococcus equi	1	0	1		
Streptococcus oralis/mitis/pneumonieae	14	11		1	2
Streptococcus parasanginis	2	2			
Streptococcus salivarius	2	2			
Trichosporon asahii	2	2			
	378	**319**	**24**	**23**	**12**

Table 2 Microorganisms with discordance between both methods

Rapid method (Simon et al) [10]	Standard method (Romero-Gómez et al) [9]	Identification by grown colony
Staphylococcus capitis	*Staphylococcus haemolyticus*	*Staphylococcus haemolyticus*
Streptococcus alactolyticus	*Streptococcus gallolyticus*	*Streptococcus gallolyticus*
Staphylococcus pseudintermedius	*Candida albicans*	*Candida albicans*

RESULTS

A total pf 582 samples from 499 patients were applied over a five-month period. The period was divided in two phases. The first phase included 382 samples. 378 were monomicrobial, of which 225 (58%) contained Gram-positive organisms and 141 (37%) contained Gram-negative organisms. Four samples from mixed and sterile cultures (false positive blood cultures) were excluded from the study. The second phase included 200 samples. 193 were monomicrobial, of which 115 (59%) contained Gram-positive and 78 (40%) contained Gram-negative organisms. Seven samples from mixed and sterile cultures (false positive blood cultures) were excluded from the study too**.** During the first phase, both methods were compared, obtaining the results presented in Table 1. Identification percentages observed for rapid method and standard method were very similar, 90.74% and 90.47% respectively. Combining the results from both methods, we achieved an identification of the 96.82% (366). Only 12 microorganisms remained unidentified and they had to be identified from the grown colony. We only observed three discrepancies between both methods (Table 2). Final identification was performed from the grown colony. During the second phase we checked the identification percentage by performing consecutively both methods. We performed in the first place rapid method (the Simon *et al*. method) to reduce processing time. We observed a 98% of correct microorganisms identifications in less than one hour and a half since blood culture was identified as positive (Table 3).

DISCUSSION

Bloodstream infections are major cause of morbidity and mortality among hospitalized patients worldwide. Early identification of microorganisms from blood culture can facilitate earlier optimization of treatment [11]. The goal of integrating quicker diagnostic microbiology laboratory techniques (ie, pathogen identification and sensibility testing) with antimicrobial stewardship practices is to improve outcomes among

Table 3 Distribution of identifications during phase two

Microorganisms	Total	Rapid method (Simon et al) [10]	Standard method (Romero-Gomez et al) [9]	Id from colony
Achromobacter xylosoxidans	1	1		
Acinetobacter baumannii	1	1		
Acinetobacter pittii	1	1		
Candida tropicalis	1	1		
Citrobacter freundii	1	1		
Clostridium ramosus	1	1		
Corynebacterium striatum	1	1		
Cutibacterium acnes	1	1		
Enterobacter cancerogenus	1	1		
Enterobacter cloacae	4	2	1	1
Enterobacter hormaechei	1	1		
Enterobacter kobei	4	4		
Enterococcus faecalis	6	6		
Enterococcus faecium	1	1		
Escherichia coli	29	29		
Gardnerella vaginalis	1	1		
Haemophilus influenzae	2	2		
Haemophilus parainfluenzae	4	3	1	
Klebsiella oxytoca	1	1		
Klebsiella pneumoniae	13	13		
Proteus mirabilis	5	5		
Pseudomonas aeruginosa	6	6		
Rothia dentocariosa	1	1		
Serratia marcescens	2	2		
Staphylococcus aureus	21	21		
Staphylococcus epidermidis	34	29	4	1
Staphylococcus haemolyticus	10	7	2	1
Staphylococcus hominis	23	22		1
Staphylococcus lugdunensis	1	1		
Staphylococcus simulans	1	1		
Streptococcus constellatus	3	3		
Streptococcus gordonii	1	1		
Streptococcus oralis/mitis/pneumoniae	2	2		
Streptococcus pyogenes	5	5		
Streptococcus salivarius	1	1		
Streptococcus sanguinis	1	1		
Veillonella rogosae	1	1		
	193	**181**	**8**	**4**

Table 4 **Comparison of the percentages of identification between the different protocols described in the bibliography.**

	GNB	GPC	*Staphylococcus aureus*	Coagulase-negative *staphylococci*	Processing time minutes
Combination of methods	98,68	97,25	100	100	<60
Simon et al. 2019 [10]	90,5	75,6	94,9	75,5	10
Romero-Gomez et al. 2012 [9]	97,7	97,84	75,8	63,3	60
Yuan Y. et al. 2020 [22]	91,5	88,3	95,7	N	30
Azrad et al. 2019 [4]	95	92	100	93	15
McIver et al. 2018 [15]	91,1	82	N	93	10
Lin Jung-Fu et al. 2018 [16]	85	78,2	88,2	N	10
Zhou et al. 2017 [17]	92,8	82,4	100	95,7	60
Barninis et al. 2016 [18]	97,5	96,1	94,11	98	60
Jakovljev et al. 2015 [19]	91	74,4	100	57,14	25
Monteiro et al. 2015 [20]	99	86,3	100	80	N
Ferreira et al. 2011 [21]	98,3	93,9	30,6	71,9	50

GNB: Gram-negative bacilli, GPC: Gram-positive cocci. N: No data

hospitalized patients. Earlier initiation of active, targeted antimicrobial therapy, informed by quicker identification and susceptibility results, has demonstrated improved patient care outcomes (decreased LOS, decreased mortality) and reduced health care expends in bloodstream infections [12]. For septic patients, delaying the initiation of antimicrobial therapy or choosing an inappropriate antibiotic can considerably worsen their prognosis [13]. With the combination of quicker diagnostic methods, we achieved the identification of 98% of the microorganisms in less than one hour and a half. We have observed an increase in the percentages of identification compared to others published in the literature (Table 4). The combination of two methods increased the percentages of microorganisms´ identification in a global manner. In our study, the biggest increase was observed with the coagulase negative staphylococci with an identification of 100% compared to 75.5% for Simon *et al* [10] and 63.3% for Romero-Gomez *et al* [9]. For *S. aureus* we obtained a percentage of identification of 100%. This allowed us to optimize the molecular diagnosis of methicillin-resistant *Staphylococcus aureus* (MRSA). We are currently performing molecular MRSA test only in confirmed *S. aureus*. Before the implementation of this combination of methods, in suspicion of *S. aureus* infections with no direct blood culture identification, we performed molecular test to anticipate methicillin resistance. This procedure, sometimes reported false methicillin resistance results due to the identification the next day of coagulase negative staphylococci in agar plates.

Another advantage of our combining both methods is the identification of contaminating organisms (coagulase negative staphylococci mainly) from positive blood cultures. This can be beneficial for patient outcomes, drug interactions and adverse events, avoiding unnecessary anti-Gram-positive antibiotic therapy. Early confirmation of contaminated blood cultures is an advantage and can lead to potential de-escalation of antibiotics along with complimentary diagnostic testing and shortening of hospital stay. The correct identification of coagulase negative staphylococci is also an improvement on the neonatal diagnosis of related catheter sepsis and the clinical significance of these isolates [14].

Finally, we would also like to acknowledge the study has some limitations. The first limitation is the direct yeast identifications. We only performed 14 yeasts direct identifications, obtaining an 84% of correct identifications. Due to the low number of isolates, we cannot conclude that this combination of methods is as good as it seems in the case of direct identification of yeasts. The second limitation is the number of isolates identified correctly in the second phase by the Romero *et al.* methodology [9]. We only need to perform this methodology in 8 isolates. This could be due to the technical staff acquired experience performing the Simon *et al.* method [10]. On the other hand, combining results by both methods with the phase one isolates, the 96.82% of the isolates were correctly identified. Therefore, we demonstrated in the whole period of the study, an improvement in direct identification from positive blood cultures combining both methods. Another of the limitations that we observed was the variability of the results depending on the experience of the worker. An example of this was the difficulty in identifying species such *Streptococcus* spp. (*S. anginosus, S. dysgalactiae* and *S. gallolyticus*) during phase one which improved significantly with experience in the technique during phase two. During the study period we did not find any anaerobic microorganisms, which was a limitation when checking the identification of this type of microorganisms.

Our combination of methods has the advantage of being a quick and easy-to-perform procedure. This combination could provide an alternative approach to improve blood culture management in microbiology laboratories without added labor to the workflow. This provides additional time for the technical staff to devote to other areas within the microbiology laboratory such as quality control, equipment maintenance or research. In conclusion, both methods combined are better than individually. We achieved an optimization of the identification of microorganisms directly from positive blood cultures by MALDI-TOF. This combination identified 98% of the microorganisms in an interval of ten minutes to one hour and a half since the blood culture flagged positive.

This practice allows a reliable and fast identification to make a clinical decision for antimicrobial treatment in bacteremia / sepsis / septic shock, improving the effectiveness of the methods performed individually.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Efficacy and safety of outpatient parenteral antibiotic therapy in patients with infective endocarditis: a meta-analysis

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ABSTRACT

Background. To investigate the clinical outcome of patients with infective endocarditis (IE) during and after outpatient parenteral antimicrobial treatment (OPAT), and to further clarify the safety and efficacy of OPAT for IE patients.

Methods. Through December 20, 2021, a total of 331 articles were preliminarily searched in Pubmed, Web of Science, Cochrane Library and Embase, and 9 articles were eventually included in this study.

Results. A total of 9 articles comprising 1,116 patients were included in this study. The overall mortality rate of patients treated with OPAT was 0.04 (95% CI, 0.02-0.07), that means 4 deaths per 100 patients treated with OPAT. Separately, mortality was low during the follow-up period after OPAT treatment, with an effect size (ES) of 0.03 (95%CI, 0.02-0.07) and the mortality of patients during OPAT treatment was 0.04 (95% CI, 0.01-0.12). In addition, the readmission rate was found to be 0.14 (95% CI, 0.09-0.22) during the follow-up and 0.18 (95% CI, 0.08-0.39) during treatment, and 0.16 (95% CI, 0.10-0.24) for patients treated with OPAT in general. Regarding the relapse of IE in patients, our results showed a low overall relapse rate, with an ES of 0.03 (95% CI, 0.01-0.05). In addition, we found that the incidence of adverse events was low, with an ES of 0.26 (95% CI, 0.19-0.33).

Conclusion. In general, the incidence of adverse events and mortality, readmission, and relapse rates in IE patients treated with OPAT are low both during treatment and follow-up period after discharge, indicating that OPAT is safe and effective for IE patients. However, our study did not compare routine hospitalization as a control group, so conclusions should be drawn with caution. In order to obtain more scientific and rigorous conclusions and reduce clinical risks, it is still necessary to conduct more research in this field and improve the patient selection criteria for OPAT treatment, especially for IE patients. Finally, clinical monitoring and follow-up of OPAT-treated patients should be strengthened.

Keywords: outpatient parenteral antimicrobial therapy (OPAT), infective endocarditis (IE), meta-analysis

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Eficacia y seguridad del tratamiento antibiótico domiciliario endovenoso en pacientes con endocarditis infecciosa: un metaanálisis

RESUMEN

Introducción. Investigar el resultado clínico de los pacientes con endocarditis infecciosa (EI) durante y después del tratamiento antibiótico domiciliario endovenoso (TADE), y determinar la seguridad y eficacia del TADE para los pacientes con EI.

Métodos. Hasta el 20 de diciembre de 2021, se realizaron búsquedas preliminares en un total de 331 artículos en Pubmed, Web of Science, Cochrane Library y Embase, y finalmente se incluyeron 9 artículos en este estudio.

Resultados. Se incluyeron un total de 9 artículos con 1.116 pacientes. La tasa de mortalidad global de los pacientes tratados con TADE fue de 0,04 (IC95%: 0,02-0,07), lo que significa 4 muertes por cada 100 pacientes tratados con TADE. Por separado, la mortalidad fue baja durante el período de seguimiento después del tratamiento con TADE, con un tamaño del efecto (TE) de 0,03 (IC95%: 0,02-0,07) y la mortalidad de los pacientes durante el tratamiento con TADE fue de 0,04 (IC95%: 0,01-0,12). Además, se encontró que la tasa de readmisión fue de 0,14 (IC95%: 0,09-0,22) durante el seguimiento y de 0,18 (IC95%: 0,08-0,39) durante el tratamiento, y de

0,16 (IC95%: 0,10-0,24) para los pacientes tratados con TADE de forma global. En cuanto a la recaída de la EI en pacientes, nuestros resultados mostraron una baja tasa global de recaída, con un TE de 0,03 (IC95%: 0,01-0,05). Además, se encontró que la incidencia de eventos adversos fue baja, con una TE de 0,26 (IC95%: 0,19-0,33).

Conclusiones. En general, la incidencia de eventos adversos y las tasas de mortalidad, reingreso y recaída en pacientes con EI tratados con TADE son bajas tanto durante el tratamiento como durante el período de seguimiento después del alta, lo que indica que el TADE es seguro y efectivo para los pacientes con EI. Sin embargo, nuestro estudio no comparó la rutina de hospitalización como grupo de control. Todavía es necesario realizar más investigaciones en este campo y mejorar los criterios de selección de pacientes para el TADE, especialmente en los pacientes con EI. Por último, se debe reforzar la monitorización clínica y el seguimiento de los pacientes tratados con TADE.

Palabras clave: tratamiento antibiótico domiciliario endovenoso, endocarditis infecciosa, metanálisis

INTRODUCTION

Infective endocarditis (IE) is a serious infectious disease with significant associated mortality, and morbidity and results in considerable medical burden to patients. The common pathogenic bacteria causing IE include *Staphylococcus* spp (*Staphylococcus aureus* predominates), *Streptococcus* spp and *Enterococcus* spp, and by other less common organisms such as the HACEK Gram-negative bacilli *(Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae)* and fungi (*Candida* spp*, Aspergillus* spp) [1-4]. The annual incidence of IE is 3-7 cases per 100,000 population, and, despite advances in diagnosis and treatment, mortality in IE patients remains high, with a reported mortality rate of 15-20% in hospital and about 40% per year during follow-up [5-7]. Patients with IE may experience serious complications early, including arterial embolism, infectious metastasis to different organs, and the development of acute heart failure, all of which are major causes of death and the most common cause of emergency valve surgery [7]. Treatment of this complex and serious disease is based on the use of appropriate antibiotics, early detection of complications, and cardiac surgery when appropriate [7].

Outpatient parenteral antimicrobial therapy (OPAT) refers to the monitored administration of parenteral antibiotics in non-inpatient or outpatient settings (*e.g.*, clinic, home, office), and besides shortening the duration of hospitalization, a major reason for OPAT use that it is a strategy to conserve antibiotic expenditures [1,8]. OPAT can be used to treat a wide variety of infections, including skin and soft tissue infections, bone and joint infections, endocarditis, gram-positive bacteremia, increasingly, drug-resistant gram-negative infections, and other specific fungal infections (e.g., cryptococcosis, candidiasis), viral infections (e.g., cytomegalovirus), or protozoa infections (e.g., Leishmania) [8]. Numerous previous studies have shown that OPAT is safe and effective for the treatment of IE [9-17]. A study by Kortajarena *et al.* sreported that only 1 in 194 patients diagnosed with IE died during follow-up after medication [9]. In addition, a propsective cohort study by Perica *et al.* found that the mortality of patients in the OPAT group was significantly lower than that in the control group during the follow-up period of one year after discharge [10]. OPAT is commonly used to consolidate antimicrobial therapy after initial hospitalization and, despite its benefits, it may increase clinical risk due to reduced clinical supervision and monitoring [11]. In addition, studies indicate that even with careful patient selection and a multidisciplinary team-driven treatment plan, the use of potentially toxic antimicrobials and the duration of treatment mean that complications, including treatment failure, and readmission of some patients managed through OPAT are inevitable [11].

Considering the therapeutic effect of OPAT on IE patients and the possible increased clinical risk, and no meta-analysis has been found, we conducted this study to explore the clinical outcome of IE patients after OPAT treatment, and further clarify the safety and efficacy of OPAT in IE patients.

MATERIAL AND METHODS

Search strategy. We searched scientific and medical databases Pubmed, Web of Science, Embase and Cochrane Library for relevant literature, and restricted the language to English. Search terms included "OPAT" , "outpatient parenteral antimicrobial therapy (OPAT)", "infective endocarditis (IE)". Through December 20, 2021, 331 studies were retrieved. After the initial screening, the full text was further read to select the studies that could be included. 331 studies were obtained in the preliminary retrieval. Among which, 179 were duplicates, 113 were irrelevant or contained no relevant data, 26 were reviews or conference abstracts, 4 were letters or case reports and were excluded, ultimately including a total of 9 articles (Figure 1). The selection of studies was carried out by two researchers. If the studies selected by them were inconsistent, they would check the studies selected by the other side and focus on the discussion to determine the final literature that could be included.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) P (patients): the subjects were patients diagnosed with IE; ii) I (intervention): outpatient parenteral antimicrobial therapy; iii) O (outcome): readmission for any cause, all-cause mortatily, IE relapse, and adverse events during the treatment or follow-up period.

Exclusion criteria were as follows: i) irrelevant to the research direction or without relevant data; ii) reviews or meeting abstracts; iii) duplicate studies; iv) letters or case reports.

Data Extraction. In this study, the data collected included: the name of the first author, year of publication, total number of subjects, number of IE deaths, readmission recurrence, and number of adverse events during OPAT the treatment and follow-up period.

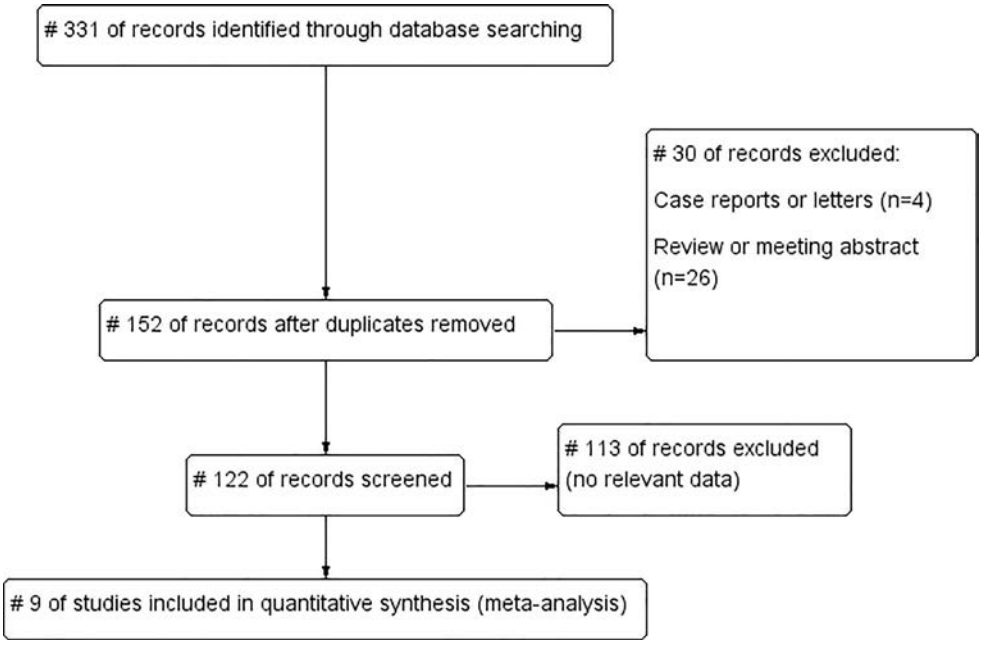

Figure 1 Study screening flow chart

Table 1 Quality assessment of 5 cohort studies

Study, year [reference]	1	2	3	4	5	6	7	8	Total score
Kortajarena, 2017 [9]	1	1	1	1	2	1	1	1	9
Pericà, 2019 [10]	1	1	1	1	2	1	1	1	9
Htin, 2013 [12]	1	1	1	1	2	1	NA	NA	7
Pajarón, 2017 [13]	1	1	1	1	2	1	NA	NA	7
Cervera, 2011 [15]	1	1	1	1	2	1	1	1	9

1 Selection of the exposed cohort; 2 Selection of the non-exposed cohort; 3 Ascertainment of exposure; 4 Demonstration that outcome of interest was not present at start of study; 5 Comparability of cohorts on the basis of the design or analysis; 6 Assessment of outcome; 7 Was follow-up long enough for outcomes to occur; 8 Adequacy of follow up of cohorts. NA=not available

Quality assessment of included studies.

a) Quality assessment of 5 cohort studies [9,10,12,13,15]:

The Newcastle-Ottawa Scale (NOS) was used to perform quality assessment (Table 1). The results revealed that 3 cohort studies showed 9 points, and 2 cohort studies showed 7 points. The articles by Htin *et al* [12] and Pajarón *et al* [13] did not describe the results during follow-up period.

b) Quality assessment of 4 retrospective analysis studies [11,14,16,17]:

The Joanna Briggs Institute critical capital checklist for students reporting progress data [18] was used to evaluate the quality of the 4 retrospective analysis studies, the results are shown in Table 2.

Statistical analysis. This study aims to discuss the clinical outcome of IE patients treated with OPAT, further clarify the safety and effectiveness of OPAT for IE patients, and then compare with the previous hospital-based Antibiotic treatment (HBAT). All statistical analyses were performed using the Stata 14.0 software (Stata corporation, College Station, TX, USA) to calculate and analyze the mortality, readmission and relapse rate of IE patients after OPAT treatment. A 95% confidence interval (95% CI) was used to determine the statistical

Table 2 Quality assessment of 4 retrospective analysis studies.

Study, year [reference]	1.Was the sample frame appropriate to address the target population?	2. Were study participants recruited in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and setting described in detail?	5. Was data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Appropriate statistical analysis?	9. Was the response rate adequate?
Durojaiye, 2021 [11]	Y	N	Y	Y	Y	Y	Y	Y	Y
Partridge, 2012 [14]	N	N	N	Y	Y	Y	Y	Y	Y
Lacroix, 2014 [16]	Y	N	N	Y	Y	Y	Y	Y	Y
Amodeo, 2009 [17]	N	N	Y	Y	Y	Y	Y	Y	Y

Y=yes; N=no.

Table 3 The basic information of the included literature.

Study, year [reference]	Study design	Treatment period			Follow up period			Total (n)	Adverse events (n)
		Mortality (n)	Relapse (n)	Readmission (n)	Mortality (n)	Relapse (n)	Readmission (n)		
Kortajarena, 2017 [9]	Cohort Study	-	-	-	1	-	35	194	-
Pericà, 2019 [10]	Cohort Study	-	-	-	33	6	47	429	-
Durojaiye, 2021 [11]	Retrospective analysis	-	-	41	4	8	-	146	-
Htin, 2013 [12]	Cohort study	2	2	3				68	-
Pajarón, 2017 [13]	Cohort study	0	3	6	-	-	-	54	11
Partridge, 2012 [14]	Retrospective analysis	-	-	-	1	1	4	34	12
Cervera, 2011 [15]	Cohort study	-	-	-	3	-	12	73	-
Lacroix, 2014 [16]	Retrospective analysis	1	-	6	-	-	-	18	-
Amodeo, 2009 [17]	Retrospective analysis	-	-	10	2	-	5	100	27

significance of the effect. The results of all studies (effect size (ES) values) were summarized using a random effect model.

RESULTS

Characteristics of the included studies. The characteristics of all the included studies are shown in Table 3. A total of 9 studies comprising 1,116 patients were included in this study, of which 5 described mortality, readmission and recurrence rates during OPAT treatment, and 6 described patient outcomes during follow-up.

Meta-analysis. Two studies showed low mortality during OPAT, with an ES value of 0.04 (95% CI, 0.01-0.12), and 6 studies which including 976 patients showed low mortality during the follow-up period after OPAT, with an ES value of 0.03 (95% CI, 0.02-0.07). The results of these 8 included studies involving 1062 patients showed that the overall mortality of IE patients treated with OPAT was 0.04 (95% CI, 0.02-0.07), P <0.01 (Figure 2A). In addition, 5 studies involving 386 patients was 0.18 (95% CI, 0.08-0.39) during the treatment period, and another 5 studies with 830 patients showed that the readmission rate was 0.14 (95%CI, 0.09-0.22) during the follow-up period,

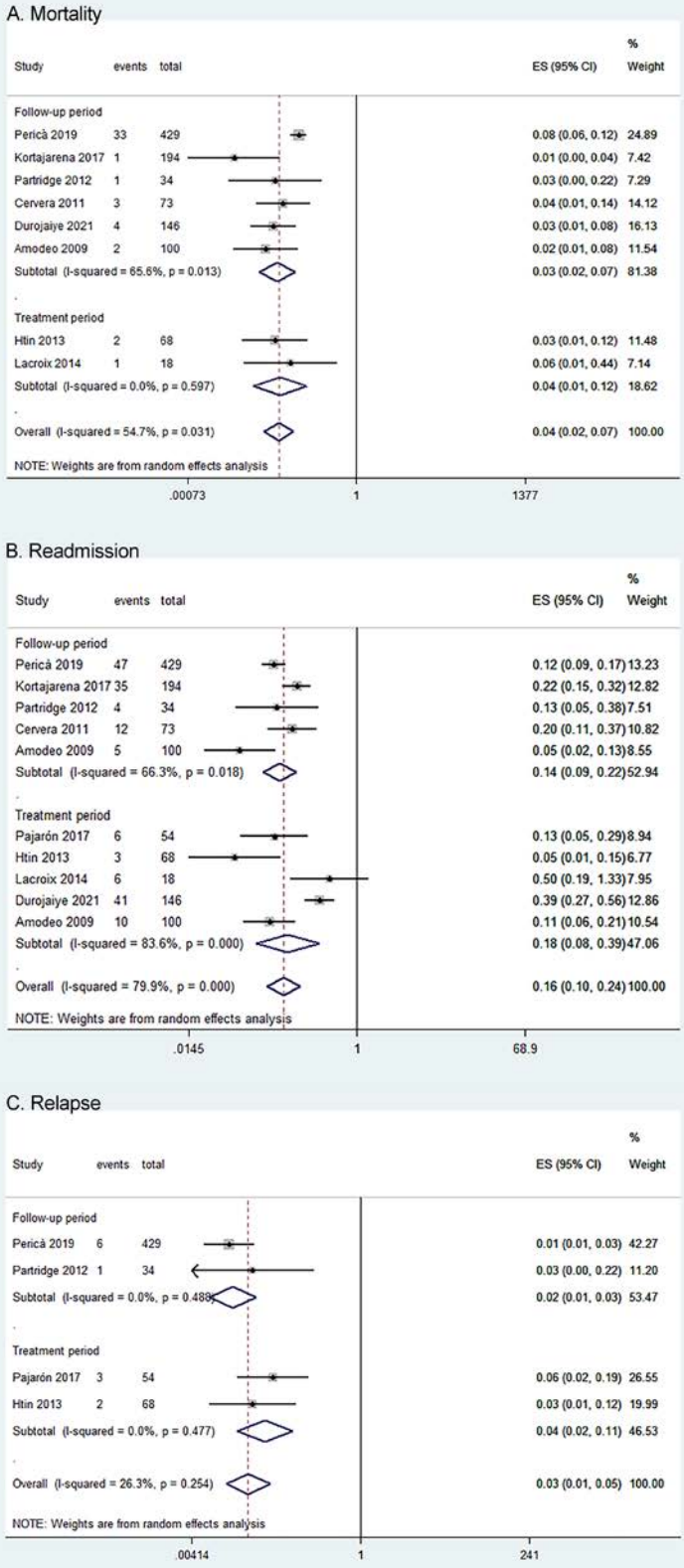

Figure 2 Forest plot of mortality (A), readmission (B), and relapse (C) rates of IE patients treated with OPAT

with an ES value of 0.16 (95% CI, 0.10-0.24) overall (Figure 2B). Regarding the relapse in IE patients, 4 included studies involving 585 patients showed a low overall relapse rate of 0.03 (95%CI, 0.01-0.05), P <0.01 (Figure 2C).

Regarding the incidence of adverse events in IE patients treated with OPAT, 3 included studies which including 188 patients showed that the incidence of adverse events was 0.26 (95%CI, 0.19-0.33), P <0.01 (Figure 3). The available data showed that the incidence of adverse events was low in patients treated with OPAT.

Funnel plot analysis showed that there was no particularly significant publication bias in the included literature (Figure 4).

DISCUSSION

A total of 9 studies were included in this study, and the results revealed that OPAT is generally effective and safe for IE patients. The overall mortality rate for patients treated with OPAT was low, namely 0.04 (95%CI, 0.02-0.07). In addition, the overall readmission and relapse rates of IE patients were low, namely 0.16 (95%CI, 0.10-0.24) and 0.03 (95%CI, 0.01-0.05), respectively. Our results are similar to those of previous studies. A study by Htin *et al.* showed that of 68 patients treated with OPAT, 2 recurred and 2 died, with a one-year survival rate of 96% [12]. Current research data show that OPAT has a good therapeutic effect on IE patients, and it is expected that OPAT will continue to show a good effect in the treatment of IE patients in the future. OPAT has also shown many benefits, such as providing significant cost effectiveness to inpatient management [1,13,16,19,20], not only by reducing the cost of treatment for patients, but also by bringing benefits to the healthcare delivery system. A study from Europe showed that the use of OPAT therapy for IE reduced costs by approximately €15,000 per patient [16]. Also, Goenaga *et al.* noted that OPAT reduced the burden of IE on hospital resources, beds and the limited time of health professionals [21]. In addition, outpatient treatment has been shown to reduce hospital-acquired complications, such as hospital-acquired infections, venous thromboembolism, and stress injuries [8,14,15]. Although OPAT has many benefits, the morbidity and mortality of IE and its limited experience in OPAT treatment mean that the candidate patients are selected carefully. Therefore, the mortality and recurrence rate of OPAT may be much lower than that of patients receiving conventional inpatient treatment. The available results showed that OPAT is relatively safe and effective for IE, however, more studies are needed to compare OPAT with routine hospitalization for IE patients (such as HBAT).

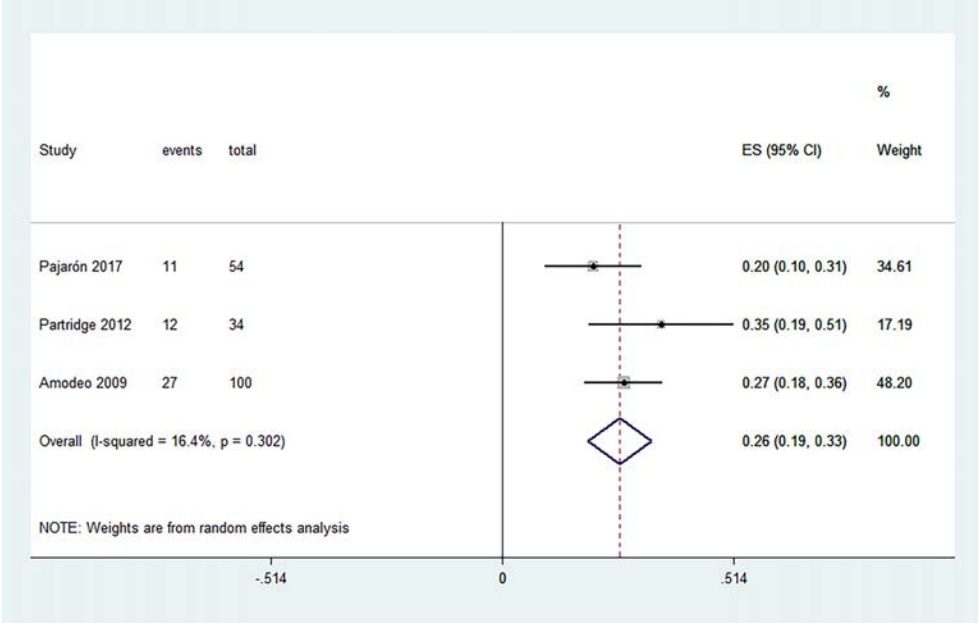

Figure 3 | **Forest plot of adverse events rates of IE patients treated with OPAT**

Most OPATs follow two main models: First, infusion in the patient's home, which is called "health care professional outpatient parenteral antimicrobial therapy (H-OPAT)", with active caregiver intervention. Second, "self-service outpatient parenteral antimicrobial therapy (S-OPAT)", in which healthcare personnel initially train patients and/or their caregivers in the use of antimicrobial agents, so the physical presence of healthcare personnel at home during infusion is subsequently unnecessary [13,22]. In the above two modes of OPAT services, the relationship between patients and medical staff is not very close. Although our results showed the effectiveness of OPAT in IE patients and the incidence of adverse events was low, many IE patients still experienced adverse events with an ES vale of 0.26 (95%CI, 0.19-0.33). Therefore, it may be necessary to strengthen the monitoring of patients with these two modes of OPAT services. Besides, there is a third type that applies in the case of patients with IE, consisting of a first phase of hospital treatment that gives way to OPAT in a series of very selected patients.

Previous studies have shown that patients treated with OPAT receive less intensive observation than hospitalized patients, and OPAT may increase clinical risk unless there are clear standards and protocols for patient supervision consistent with existing national and international practice guidelines [11,14]. Durojaiye *et al.* found that pre-existing renal failure and comorbidities (Charlson comorbidity index score) were strongly associated with OPAT treatment failure. Also, patients with a prior history of IE and cardiac complications, such as severe valvular insufficiency, perivalvular abscesses, or internal cardiac fistula, were more likely to have poorer long-term outcomes [11]. Moreover, studies have shown that endocarditis patients with artificial heart valves, consistently positive blood culture results, poorly controlled congestive heart failure, large neoplasms (>10 mm in length), recurrent embolic events, *S. aureus* etiology, or conduction abnormalities are at increased risk for clinical complications, and therefore inpatient treatment or daily outpatient follow-up during the first 2 weeks of treatment is recommended [22-24]. Andrews *et al.* recommended that patients with uncomplicated endocarditis caused by viridans group streptococci be discharged from hospital after 1 week to receive OPAT treatment [24]. Therefore, it is very important to select the right IE patients for OPAT at the right time. Furthermore, it is also necessary to strengthen the monitoring and follow-up of IE patients treated with OPAT, including monitoring the patients' vital signs, complications and relevant laboratory indicators to reduce the occurrence of adverse events. Especially for patients receiving OPAT in the community center or at home, establishing a robust approach to patient monitoring and review is critical [8]. A study has shown that the OPAT Medical Service has established procedures for routine and emergency examination of patients [14]. At Sheffield in the UK, patients are followed up in the OPAT ward at least once a week, this frequent clinical contact facilitates the early detection of complications or clinical deterioration[14], tthereby reducing the rate of recurrence and mortality. Finally, it is critical to develop a well-trained OPAT team. Overall, we believe that the benefits of OPAT in the treatment of IE patients outweigh the disadvantages.

This study has some shortcomings. First, we only included English literature, and thus many non-English reports may

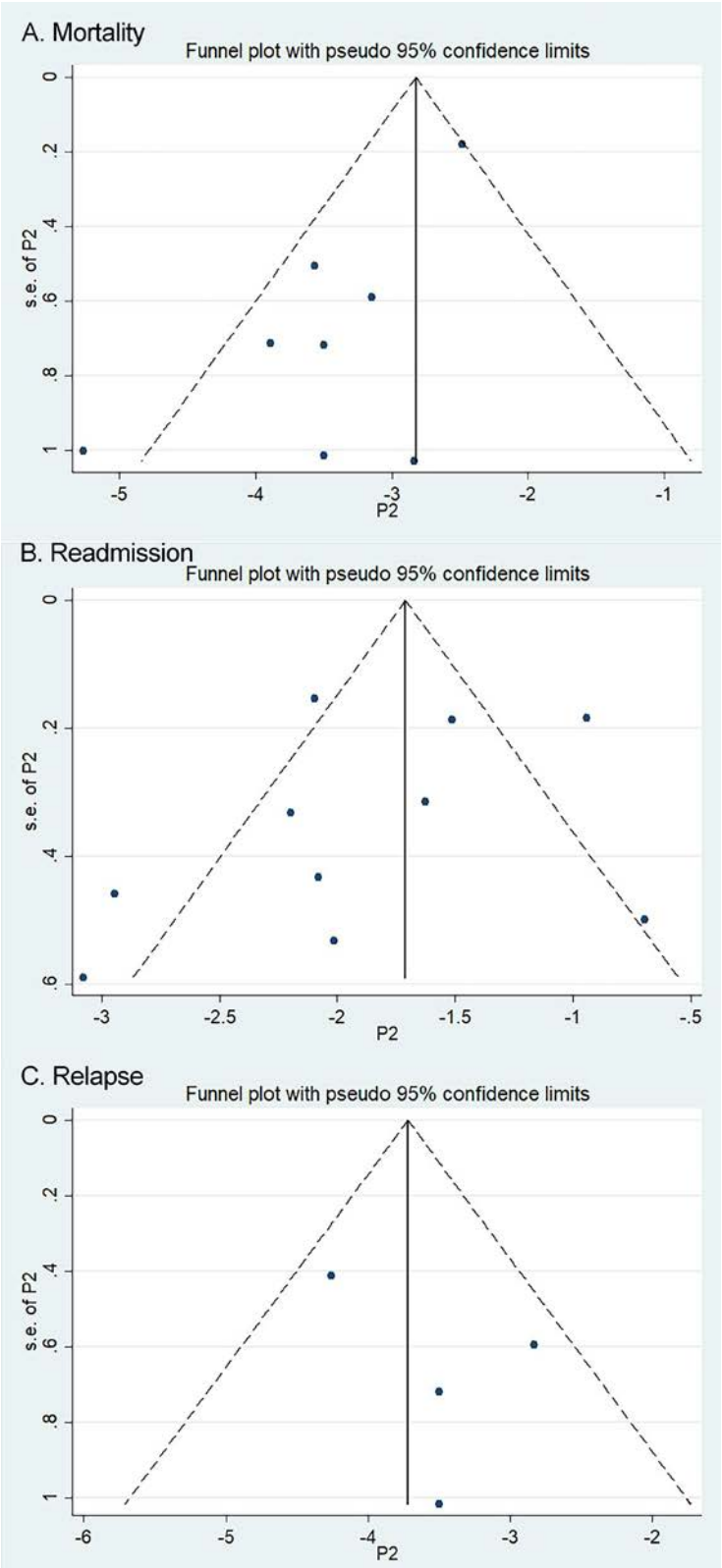

Figure 4 | **Funnel plot of the included literatures: mortality (A), readmission (B), and relapse (C).**

be omitted. Second, there was no specific data on the sex differences, age and underlying diseases of patients in the included studies, so there was no subgroup analysis in this respect, and the influence of these confounding factors on the study results cannot be excluded. Finally, since not all articles included data during OPAT treatment and follow-up after discharge, it was impossible to compare the clinical outcomes during treatment and follow-up. In addition, the data on adverse events of OPAT are too few, and the number of patients included for the variable adverse effects is really low, thus more research data are still needed to confirm the safety of OPAT.

In general, the mortality, readmission, and relapse rates and incidence of adverse events in IE patients treated with OPAT are low both during treatment and follow-up after discharge, indicating that OPAT is safe and effective for IE patients. However, our study did not compare routine hospitalization as a control group, so conclusions should be drawn with caution. In order to obtain more scientific and rigorous conclusions and reduce clinical risks, it is still necessary to expand research in this field and improve the patient selection criteria for OPAT service, especially for IE patients, prudent and selective use of OPAT may produce optimal treatment effects for patients. Finally, clinical monitoring and follow-up of patients treated with OPAT should be strengthened.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Eficacia en vida real del cambio a bictegravir/emtricitabina/tenofovir alafenamida en pacientes previamente tratados con pautas triples que contienen rilpivirina

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RESUMEN

Objetivo. Analizar la eficacia y tolerabilidad de la estrategia de cambio desde regímenes basados en rilpivirina (RPV) a bictegravir/emtricitabina/tenofovir alafenamida (B/F/TAF) en la vida real.

Métodos. Estudio unicéntrico, observacional y retrospectivo. Se seleccionaron pacientes que cambiaron de un régimen con RPV a B/F/TAF antes de febrero del 2020 analizándose los resultados después de 24 y 48 semanas. Se determinó el porcentaje que permanecía con carga viral indetectable, así como los cambios en linfocitos CD4+, parámetros metabólicos y función renal.

Resultados. Se incluyeron en el estudio 42 pacientes. 32 de los 35 (91,4%) que completaron las 48 semanas de seguimiento tenían carga viral indetectable. El recuento de linfocitos CD4+ permaneció estable a las 24 y a las 48 semanas. El tipo de análogos recibidos previamente no influyó en la respuesta

Conclusión. El cambio desde una triple terapia con RPV a B/F/TAF es una estrategia segura y eficaz en la vida real.

Palabras clave: Bictegravir; vida real; Rilpivirina; interacciones medicamentosas; VIH

Real-world efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in pretreated patients with triple therapy containing rilpivirine

ABSTRACT

Objective. To analyze the efficacy and tolerability of the strategy to change from rilpivirine (RPV) based regimens to bictegravir / emtricitabine / tenofovir alafenamide (B/F/TAF).

Methods. Single-center, observational and retrospective study. Patients who made the change to B/F/TAF before February 2020 were selected, analyzing the results after 24 and 48 weeks. The percentage that remained with an undetectable viral load was determined, as well as the changes in CD4 + lymphocytes, metabolic parameters and renal function.

Results. A total of 42 patients were included. Thirty-two of the 35 patients (91.4%) who completed the 48 weeks of follow-up had an undetectable viral load. The CD4 + lymphocyte count remained stable at 24 and 48 weeks. The response to B/F/TAF was not influenced by the two analogs previously received.

Conclusion. Switching from triple therapy with RPV to B/F/TAF is a safe and effective strategy in real life.

Palabras clave: bictegravir; real-world; rilpivirine; drug interactions; HIV

INTRODUCCIÓN

Bictegravir es un nuevo inhibidor de la integrasa comercializado coformulado como bictegravir/emtricitabina/tenofovir alafenamida (B/F/TAF) aprobado para el tratamiento del VIH-1 en adultos naïve y pretratados [1]. B/F/TAF en pastilla única ha demostrado múltiples beneficios: es una pauta segura y eficaz, tiene una alta barrera genética, presenta pocas interacciones medicamentosas, origina mejoría de parámetros metabólicos si el cambio es a partir de un inhibidor de la proteasa

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potenciado (IPp), hay datos que sugieren una menor toxicidad neurológica que otros inhibidores de la integrasa y es activo frente al virus de la hepatitis B [2-4].

La mayoría de los estudios de simplificación demuestran eficacia del cambio a partir de dolutegravir o de un IPp, pero son pocos los datos que se tienen tras el cambio de pautas basadas en rilpivirina (RPV) [3,5]. Por ello, diseñamos este estudio cuyo objetivo es analizar la eficacia y tolerabilidad de la estrategia de cambio desde regímenes basados en RPV a B/F/TAF en la práctica clínica.

MATERIAL Y MÉTODOS

Estudio unicéntrico, observacional y retrospectivo diseñado para describir la eficacia, seguridad y tolerabilidad de cambiar a B/F/TAF desde un tratamiento triple basado en RPV. Se revisó la base de datos de los 4.397 enfermos en seguimiento en el Hospital Universitario La Paz de Madrid y se seleccionaron aquellos con al menos 6 meses de seguimiento y que hicieron el cambio antes de febrero del 2020 analizándose los resultados tras 24 y 48 semanas. El protocolo fue aprobado por el Comité Ético que autorizó no firmar consentimiento informado por ser un estudio retrospectivo basado en práctica clínica. El objetivo primario fue analizar la proporción de pacientes con carga viral indetectable (<50 copias/mL) por intención de tratar (ITT) y por protocolo (PP) en las semanas 24 y 48. En el análisis por ITT se incluyeron todos los pacientes que recibieron al menos una dosis de B/F/TAF. En el análisis PP se excluyeron los perdidos o que cambiaron por causa diferente al fracaso virológico. Los objetivos secundarios fueron el porcentaje y causa de interrupción de B/F/TAF y el cambio en el recuento de linfocitos CD4+ y en los parámetros metabólicos y de función renal.

Los resultados obtenidos se expresan en número absoluto (porcentaje) o mediana (rango intercuartílico). Se utilizó el test de Wilcoxon para determinar si existieron cambios significativos en las variables cuantitativas entre la determinación basal y las semanas 24 y 48. Se analizó si hubo diferencias en el porcentaje de pacientes con carga viral indetectable dependiendo de si venían de una pauta con TAF o TDF mediante la prueba de chi-cuadrado y las diferencias en los cambios de CD4+, colesterol y creatinina mediante pruebas no paramétricas.

Tabla 1 Características basales de los 42 pacientes que cambiaron a B/F/TAF desde pautas con RPV

Edad mediana en años	49,5 (43,8-55,4)
Varón/mujer	35 (83,3%) /7 (16,7%)
Raza caucásica	33 (78,6%)
Vía de transmisión del VIH	
HSH	22 (52,4%)
UDVP	10 (23,8%)
HTX	7 (16,7%)
Desconocido	3 (7,1%)
Años de infección VIH	19,3 (9,8-28,3)
Hepatitis crónica por virus B	2 (4,8%)
Hepatitis C curada	13 (31%)
Carga viral <50 copias/mL	34 (80,9%)
Nadir de linfocitos CD4+ µL (RIQ)	233 (157-332)
Linfocitos CD4+ basales µL (RIQ)	819 (420-966)
Resistencias archivadas	
M184V	1 (2,3%)
K65R,V90I	1 (2,3%)
D67G,T69N,K70R,L74I,K103N,M184V,G190A, K219Q	1 (2,3%)
Tratamiento antirretroviral previo	
RPV/F/TAF	15 (35,7%)
RPV/F/TDF	24 (57,1%)
RPV+ABC/3TC	3 (7,1%)
Motivo del cambio a B/F/TAF	
Toxicidad de la pauta previa	6 (14,3%)
Mala adherencia (dificultad de ingesta con alimento)	7 (16,7%)
Interacciones medicamentosas	19 (45,2%)
Prevención de toxicidad	7 (16,7%)
Otros	3 (7,1%)

Variables cuantitativas se dan como mediana (rango interquartil). B/F/TAF: Bictegravir/FTC/Tenofovir alafenamida; RPV: Rilpivirina; RI: rango intercuartilico; HSH: hombres que tienen sexo con hombres; UDVP: usuarios de drogas por vía parenteral; HTX: heterosexual; RPV/F/TAF: Rilpivirina/FTC/Tenofovir alafenamida; RPV/F/TDF: Rilpivirina/FTC/Tenofovir disoproxil fumarato; RPV+ABC/3TC: Rilpivirina+Abacavir/3TC

RESULTADOS

Se incluyeron 42 pacientes, 35 varones (83,3%), con una mediana de edad de 49,5 años (IQ: 43,8-55,4). La mediana del tiempo de infección era 19,3 años (IQ: 9,8-28,3). En el momento del cambio 34 pacientes (80,9%) tenían carga viral indetectable y 8 detectable (todos por falta de adherencia sin mutaciones de resistencia). La mediana de CD4+ fue de 819 células/mm^3 (420-966). En la tabla 1 se especifican las características basales de los 42 pacientes.

Los regímenes previos fueron RPV/F/TAF en 15 pacientes (35,7%), RPV/F/ tenofovir disoproxil fumarato en 24 (57,1%) y RPV + abacavir/lamivudina en 3 (7,1%). Sólo 3 pacientes tenían historia de mutaciones de resistencia: un paciente D67G,T69N,K70R ,L74I,K103N,M184V,G190A,K219Q, otro M184V y otro K65R,V90I. Ninguno tenía historia previa de resistencia a inhibidores de la integrasa. El motivo del cambio a B/F/TAF fue toxicidad ósea o renal en 6 pacientes (14,3%), prevención de esta en 7 (16,6%), dificultad de la toma de RPV con alimento en otros 7 (16,6%), para evitar interacciones medicamentosas en 19 (45,3%) y por razones dependientes del médico responsable en 3 (7,2%).

Tabla 2 **Porcentaje de pacientes con carga viral indetectable y evolución de los linfocitos CD4+ y de los parámetros metabólicos y función renal a las 24 y 48 semanas tras el cambio a B/F/TAF**

	Basal n=42	Semana 24 n=40	Semana 48 n=35	p valor
CV<50 copias/ml	34/42 (80,9%)	40/40 (100%)	32/35 (91.4%)	<0.01
Linfocitos CD4+/µL	819 (420-966)	729 (325-1003)	895 (495-1003)	0,13 (semana 24) 0,1 (semana 48)
Colesterol total (mg/dL)	171 (150-203)	187 (176-212)	186 (171-205)	<0,001 (semana 24) 0,007 (semana 48)
HDL	40 (36,75-43,259	42 (39-48)	41,5 (38,75-46,25)	0,02 (semana 24) 0,76 (semana 48)
LDL	108 (82,25-128,5)	121 (100-129)	112 (100,75-128,5)	<0,01 (semana 24) 0,01 (semana 48)
Triglicéridos	159,5 (101,75-202,25)	146 (92-252)	140 (107,25-195,25)	0,94 (semana 24) 0,78 (semana 48)
Glucosa (mg/dL)	94 (87-101)	97 (88-105)	96 (90-105)	0,86 (semana 24) 0,28 (semana 48)
Creatinina (mg/dL)	0,91 (0,84-1,15)	0,98 (0,88-1,15)	0,96 (0,86-1,12)	<0,001 (semana 24) <0,001 (semana 48)

B/F/TAF: Bictegravir/FTC/Tenofovir alafenamida; CV: carga viral

A las 24 semanas de tratamiento el porcentaje de pacientes con CV<50 fue de 92,8% (39/42) y 97,5% (39/40) en ITT y PP y las 48 semanas estos porcentajes fueron 76,2% (32/42) y 91,4% (32/35). Tres pacientes tenían CV >50 copias/ml, sin embargo, eran muy bajas (59, 60 y 112 copias/ml), y sus médicos no cambiaron el tratamiento. Siete pacientes no se incluyeron en el análisis PP en la semana 48: tres por cambio de tratamiento (dos simplificaciones a doletugravir/3TC y uno volvió a su tratamiento previo), un paciente falleció por neumonía secundaria a SARS-CoV-2 y tres no acudieron a revisión en la semana 48.

Los análogos recibidos previamente no influyeron en la respuesta en la semana 48: 92,9% (13/14) en el grupo que había recibido TAF/F, 88,9% (16/18) TDF/F y 100% (3/3) ABC/LAM; p=0,7. Los pacientes que partían de carga viral detectable tuvieron tendencia a una menor supresión en la semana 48 aunque sin diferencias significativas: 71,4% (5/7) vs 96,4% (27/28); p=0,09. El recuento de linfocitos CD4+ permaneció estable a las 24 y 48 semanas. De los dos pacientes con hepatitis crónica B, uno no acudió a la revisión de las 48 semanas y el otro continúa con B/F/TAF manteniendo ambos virus controlados.

El peso al inicio del tratamiento con B/F/TAF se cuantificó en 36 pacientes (77,9 Kg; RI: 71,4-87,6 Kg) pero a las 48 semanas sólo pudo recogerse en 7 (78,5 Kg; RI: 75,2-89 Kg).

La glucemia basal no se modificó (p=0,28) mientras que se produjeron elevaciones significativas en los niveles de creatinina (0,07 y 0,05 mg/dl), colesterol total (16 y 15 mg/dl) y LDL (13 y 4 mg/dl) tanto a las 24 como a las 48 semanas. Este aumento fue mayor en los pacientes que venían de TDF respecto a los que venían de TAF (23 mg/dl vs 11 mg/dl; p=0,03 y 25 vs -2,5; p=0,08). No se observaron diferencias clínicamente significativas en el aumento de creatinina (0,07 en semanas 24 y 48). En la tabla 2 aparecen reflejadas las modificaciones en los parámetros analíticos.

DISCUSIÓN

En nuestra cohorte el cambio a B/F/TAF desde pautas triples basadas en RPV mantuvo la supresión virológica en el 91,4% de los pacientes a la semana 48 independientemente de los 2 análogos acompañantes. El único factor que se asoció con menores tasas de supresión virológica fue tener carga viral detectable en el momento del cambio. En estos pacientes la falta de eficacia se relacionó con falta de adherencia y no con ineficacia de la pauta.

Siete pacientes no completaron el seguimiento a las 48 semanas. En ningún caso por toxicidad de B/F/TAF. En 3 se debió a pérdida de la última visita por problemas de movilidad originados por la pandemia. En los otros casos fue por simplificación, vuelta a la pauta anterior tras acabar un tratamiento con omeprazol y un fallecimiento por neumonía secundaria a SARS-CoV-2..

Aunque se ha descrito en diversas publicaciones que los inhibidores de la integrasa pueden inducir aumento de peso

[6], no se pudo establecer si el uso de B/F/TAF modificó dicho parámetro ya que sólo se recogió en 7 pacientes a las 48 semanas porque muchas de las visitas se efectuaron de forma telefónica por la situación de pandemia.

La elevación de los niveles de colesterol, aunque estadísticamente significativa, no fue clínicamente relevante y puede explicarse porque más del 50% de los pacientes cambiaron a B/F/TAF a partir de RPV/F/TDF y con ello se perdió el papel hipolipemiante del TDF [7].

Nuestro estudio tiene como importante limitación la naturaleza retrospectiva del análisis y el bajo número de pacientes incluido, pero ofrece datos del cambio desde RPV fundamentalmente para pacientes en los que se pretende evitar interacciones medicamentosas y con la alimentación. En las grandes series de cambio a B/F/TAF son pocos los pacientes que cambian a partir de un no análogo [8-10]. En el estudio en vida real de Rolle et al [11], sólo el 23% de 350 pacientes recibió B/F/TAF a partir de una pauta con 2 análogos y un no análogo sin especificar cual y en el estudio en fase 3 de Hagins et al [12] el cambio fue del 30%. Por ello, aunque el número de pacientes sea pequeño, creemos que nuestro estudio puede aportar datos sobre la eficacia y seguridad del cambio a B/F/TAF a partir de pautas triples conteniendo RPV. Además, nuestros datos, al ser en vida real, representan un sector de la población VIH muy presente en nuestras consultas que no suelen estar representados en los ensayos clínicos. En general se trata de pacientes mayores, con evolución más larga de la infección por VIH y más comorbilidades.

En conclusión, el cambio desde una triple terapia con RPV a B/F/TAF es una estrategia segura y eficaz en la vida real.

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CONFLICTO DE INTERESES

La Dra. Luz Martín Carbonero, el Dr. José Ignacio Bernardino y la Dra. Mª Eulalia Valencia declaran haber recibido compensación económica por colaboración en labores de asesoría y ayudas a la asistencia de Congresos por parte de VIIV, Gilead, Janssen y MSD. El Dr Luis Ramos y el Dr. Alejandro de Gea Grela declaran no tener ningún conflicto de interés.

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Características sociodemográficas y factores de riesgo asociados a las bacteriurias significativas en un área de salud del sudeste español

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RESUMEN

Objetivo. Determinar las características epidemiológicas de las bacteriurias significativas (BS) y su relación con factores sociodemográficos, así como analizar los factores de riesgo en pacientes hospitalizados.

Material y métodos. Estudio descriptivo transversal realizado sobre el conjunto de registros obtenidos a partir del procesamiento de todas las muestras de urocultivos recibidas en el laboratorio de Microbiología del Hospital Universitario Virgen de las Nieves (Granada, España) entre enero de 2016 y diciembre de 2020, diferenciando entre población infantil y adulta. Como variables dependientes se analizaron la presencia de BS, las variables independientes fueron la edad en años, sexo, año y mes de la muestra, tipo de muestra, procedencia de la muestra y número de aislamientos. En los urocultivos obtenidos de pacientes ingresados se evaluó la presencia de factores de riesgo asociados a partir del Conjunto Mínimo Básico de Datos.

Resultados. Se analizaron 68.587 registros válidos (un 96,3% del total). El 40,8% (IC95%: 40,4%-41,2%) de los urocultivos en adultos y el 33,8% (IC95%: 32,9%-34,7%) en niños fueron positivos. La incidencia en adultos descendió de 18,2 casos/1.000 habitantes en el año 2016 a 14,6 casos/1.000 habitantes en 2020. Para estos mismos años, la incidencia en menores disminuyó de 21,1 a 8,4 casos/1.000 habitantes, respectivamente. Los urocultivos positivos fueron más frecuentes en niños del ámbito urbano frente al ámbito rural (OR=1,37; p<0,01), sin significación en adultos. En adultos hospitalizados, por cada año de edad transcurrido, el riesgo de BS aumentó un 2%, (OR=1,02), fue un 36% mayor en mujeres (OR=1,36), un 18% superior en obesos (OR=1,18) y un 17% más frecuente en pacientes con enfermedad renal (OR=1,17), todas ellas de forma significativa (p<0,01). No se observó relación entre BS y diagnóstico de COVID-19.

Conclusión. Las características sociodemográficas de la población con BS atendida en nuestra área de salud, tanto en adultos como en niños, son similares a las encontradas en otras áreas geográficas a nivel mundial, observando una tendencia decreciente en la incidencia de BS en los años estudiados. La frecuencia de BS en niños es mayor en el ámbito urbano.

Palabras clave: bacteriuria significativa; epidemiología; factores de riesgo; incidencia; ruralidad; COVID-19

Sociodemographic characteristics and risk factors associated to significative bacteriuria in a Spanish health area

ABSTRACT

Objective. To determine the epidemiological characteristics of significative bacteriuria (SB) and their relationship with sociodemographic factors and to analyze risk factors in inpatients.

Material and methods. Cross-sectional descriptive study carried out on urine culture samples received between 2016-2020 in the Microbiology laboratory, differentiating between minors and adults. The dependent variable was the presence of SB and the independent variables were age, sex, year, type of sample and source of the sample. In urine cultures of inpatients, risk factors were evaluated from the Minimum Basic Data Set.

Results. A total of 68,587 valid records (96.3% of the total) were analyzed. 40.8% (95% CI: 40.4%-41.2%) of urine cultures in adults and 33.8% (95% CI: 32.9%-34.7%) in children were positive, with an incidence that ranged in adults between 18.2 cases/1,000 inhabitants in 2016 and 14.6 cases/1,000 inhabitants in 2020 and 21.1 and 8.4 cases/1,000 inhabitants respectively in minors. Positive urine cultures were

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more frequent in children from urban areas compared to rural areas (OR=1.37; p<0.01). In hospitalized adults, for each year of age the risk of SB increased by 2%, it was 36% higher in women, 18% higher in obese patients and 17% more frequent in patients with kidney disease, (p<0.01). No relationship was observed between SB and diagnosis of COVID-19.

Conclusion. The sociodemographic characteristics of the population with SB in our health area are similar to those found in other geographical areas worldwide, observing a decreasing trend in incidence in the years studied. The frequency of SB in children is higher in urban areas.

Key words: significative bacteriuria; epidemiology; risk factors; incidence; rurality; COVID-19

INTRODUCCIÓN

Las infecciones del tracto urinario (ITUs) representan un elevado volumen de la atención sanitaria, tanto a nivel de Atención Primaria como Hospitalaria. La prevalencia de esta infección se sitúa en el 12,9% de las infecciones hospitalarias en Estados Unidos, el 19,6% en Europa y el 24% en los países en vías de desarrollo [1], siendo en España del 16,2% [2].

Se han descrito diferentes factores de riesgo asociados a las ITUs, dependiendo de si éstas se desarrollan en el medio comunitario o en el hospitalario. En la comunidad y en adultos, la frecuencia de ITUs es mayor en mujeres no institucionalizadas y mayores de 65 años, siendo factores de riesgo importantes, entre mayores de 85 años, las fracturas vertebrales, la incontinencia urinaria, las enfermedades reumáticas y la demencia [3]. En menores de 14 años hay evidencias de mayor incidencia de ITUs según edad, sexo, raza y estado de la circuncisión en niños, siendo los menores de un año los que presentan mayores cifras [4].

Las ITUs hospitalarias se relacionan con el servicio de ingreso del paciente, siendo la primera causa de infección en unidades como psiquiatría, geriatría y cuidados intensivos, y constituyendo el sondaje urinario en esta última el principal factor de riesgo [5]. Otros estudios apuntan a una mayor incidencia de ITU en pacientes con otras patologías asociadas como diabetes mellitus, enfermedad renal o cáncer, entre otras [3]. A nivel local, los datos del estudio sobre Prevalencia de Infección Nosocomial realizado en 2019 reveló cifras del 12% de ITUs en pacientes ingresados en el Hospital Universitario Virgen de las Nieves de Granada entre el total de infecciones relacionadas con la asistencia sanitaria, siendo la prevalencia de pacientes con esta infección del 1,6% [6]. En España, la incidencia de ITUs en pacientes adultos hospitalizados ha experimentado un incremento desde el año 2001 en ambos sexos por igual, con un riesgo mayor de mortalidad en pacientes de mayor edad [7]. Más recientemente, algunos estudios apuntan a que la presencia de COVID-19 en pacientes hospitalizados puede incrementar la infección asociada a la asistencia sanitaria, y en concreto las ITUs, en pacientes sondados hasta un 43%, comparado con pacientes sin COVID-19 [8].

La mayoría de los estudios publicados coinciden en que *Escherichia coli* es el patógeno que se aísla más frecuentemente, con una incidencia global de 48 casos por 100.000 personas-año, lo que representa el 18% de los episodios de origen hospitalario y el 33% de los comunitarios [9], con una frecuencia mayor en niños que en adultos [10]. La frecuencia de ITUs puede variar en función de la época del año. Se ha observado que la incidencia en niños es menor en la época estival; sin embargo, las hospitalizaciones relacionadas con ITU, a cualquier edad, se asocian con una mayor temperatura ambiental, por lo que son más frecuentes en verano [11]. La incidencia de ITU también se asocia con el número de habitantes de una población, siendo superior en ciudades con menos de treinta mil habitantes [12].

El objetivo del presente estudio fue determinar las características epidemiológicas de las bacteriurias significativas (BS) en nuestro medio y su relación con factores sociodemográficos, así como analizar los factores de riesgo en pacientes hospitalizados en un área de referencia hospitalaria del sur de España, diferenciando entre población adulta e infantil.

MATERIAL Y MÉTODOS

Se diseñó un estudio descriptivo transversal con componente ecológico. El ámbito geográfico fue la provincia de Granada, ubicada en la Comunidad Autónoma de Andalucía, situada al sureste de España, y estructurada en cuatro distritos sanitarios: Granada, Metropolitano, Nordeste y Sur. El ámbito poblacional fue el área de referencia del Hospital Universitario Virgen de las Nieves, que abarca parte de los distritos Granada y Metropolitano, con una población de referencia de 330.486 habitantes y que cuenta con un laboratorio de Microbiología.

Este hospital es un complejo regional constituido por tres centros (Hospital General de Especialidades, Hospital Materno-Infantil y Hospital de Neuro-Traumatología y Rehabilitación) que tiene una actividad asistencial de tercer nivel. En nuestro estudio la población asistida estuvo constituida por pacientes con diagnóstico clínico de sospecha de ITU procedentes exclusivamente de atención especializada, como signo de importancia clínica, diferenciando entre sujetos hospitalizados y aquellos que accedieron al sistema a través de consultas externas o urgencias, considerando en estos dos últimos casos que las infecciones eran adquiridas en la comunidad (salvo que el paciente hubiese estado hospitalizado dentro de las 48 horas previas, en cuyo caso se consideró infección hospitalaria). La población de estudio también se diferenció por su edad (adultos y niños hasta 14 años) y por su sexo.

Las muestras fueron obtenidas mediante sondaje provisional, micción media, sonda permanente, catéter de nefrostomía o bolsa colectora, dependiendo de las condiciones clínicas de cada paciente. Para el transporte, se emplearon tubos con ácido bórico como conservante. Todas las orinas fueron cultivadas siguiendo un protocolo de trabajo establecido por el laboratorio [13]. Se empleó un asa calibrada de 1 µL y el medio de cultivo cromogénico UriSelect4 (BioRad, Barcelona, España), incubando cada muestra durante 24 horas a 37°C. Sólo en las muestras obtenidas de pacientes atendidos en el Servicio de Nefrología se añadió una placa de agar sangre de cordero (BD,

Madrid, España) que se incubó en CO_2. Tras esto, se procedió al contaje de colonias crecidas. Se utilizaron los siguientes puntos de corte: cultivo negativo (<10.000 UFC/ml en orina media o <1.000 UFC/ml en orina de sondaje provisional); cultivo positivo (bacteriuria de >100.000 UFC/ml de uno o dos uropatógenos, o entre 10.000 y 100.000 de uno solo y >10.000 UFC/ml de uno o dos uropatógenos en orina media, o entre 1.000 y 10.000 UFC/ml de uno solo en orina de sondaje provisional), o presencia de microbiota mixta (>10.000 UFC/ml de más de dos uropatógenos) [13-15]. La posterior identificación de los microorganismos aislados se realizó mediante espectrometría de masas MALDI-TOF (Biotyper, Brucker Daltonics, Billerica, EE.UU.) y/o MicroScan WalkAway (Beckman-Coulter, Brea, California).

Se definió como caso toda muestra para urocultivo analizada en el laboratorio de microbiología entre enero de 2016 y diciembre de 2020, fuese obtenida en niños (≤14 años) o en adultos (>14 años). Se excluyeron las muestras que no estuvieron claramente definidas o identificadas, así como los registros de los que no se tenía constancia de edad y sexo. No se calculó tamaño muestral, pues se seleccionaron todos los registros de los cinco años que cumplían los criterios de inclusión y exclusión. Las variables del estudio fueron las obtenidas de la base de datos de urocultivos, facilitadas por el Servicio de Microbiología por medio de MODULAB®, sistema de gestión de información de laboratorio utilizado en el Sistema Sanitario Público de Andalucía como soporte de la historia clínica electrónica, anonimizando la identidad del paciente mediante los códigos de la muestra. Como variables dependientes se analizaron la existencia de BS (sí, no) y tipo de microorganismo aislado (bacilos gramnegativos, cocos grampositivos, levaduras y otros). Como variables independientes se consideraron la edad en años, sexo (hombre, mujer), año y estación del año de recogida de muestra, tipo de muestra (tomada por sondaje provisional, sonda permanente, u otros procedimientos), procedencia hospitalaria o comunitaria (incluyendo urgencias y consultas externas) de la muestra, número de aislamientos y ámbito de residencia (rural: poblaciones de menos de 2.000 habitantes; semi-rural: de 2.000 a 9.999 habitantes; urbano: 10.000 o más habitantes) [16]. Para aquellos registros obtenidos de pacientes ingresados, se evaluó la presencia de los factores de riesgo más frecuentes a partir del Conjunto Mínimo Básico de Datos (CMBD): hipertensión arterial, diabetes mellitus II sin complicaciones, hiperlipemia, dependencia de nicotina, obesidad, neumonía, fallo renal, enfermedad pulmonar obstructiva crónica (EPOC), neoplasia maligna, insuficiencia cardíaca y diagnóstico de COVID-19. En los urocultivos procedentes de la comunidad no fue posible evaluar estos factores de riesgo ya que no siempre se recoge esta información y, de existir, no está estructurada para su análisis. Para evaluar la posible implicación del componente ecológico en el desarrollo de BS se agregaron los urocultivos según población de residencia del paciente y se tuvieron en cuenta variables sociodemográficas básicas asociadas a los municipios [17]: altitud, tasa de paro [18], tasa de natalidad, tasa de mortalidad, tasa de extranjería y renta media anual, así como la distancia al hospital más cercano.

Se realizó un análisis descriptivo de los resultados de los urocultivos mediante el cálculo de frecuencias y porcentajes para las variables cualitativas y medias y desviaciones para las cuantitativas. Se calcularon tasas de incidencia poblacionales por 1.000 habitantes/año por grupos de edad y sexo, tomando como población de referencia la del Área Hospitalaria en mitad del periodo estudiado. La comparación de medias se realizó mediante el test t de Student (con dos grupos) o análisis de la varianza (con más de dos grupos), previa comprobación de los supuestos de normalidad y homocedasticidad. Se aplicó una regresión logística multivariante con las variables que resultaron significativas o con una p<0,10 en el análisis bivariante, utilizando el procedimiento por pasos sucesivos hacia atrás de Wald, con criterio de entrada p<0,05 y criterio de salida p<0,10. En el estudio ecológico se calcularon correlaciones de Pearson para relacionar el porcentaje de BS de cada municipio con las variables sociodemográficas. Todos los análisis se realizaron de forma separada para adultos y niños. Se utilizaron los programas estadísticos R e IBM SPSS v19.0.

Al ser un estudio no intervencionista, ya que el material biológico solo se utilizó para el diagnóstico estándar de BS, sin ninguna investigación adicional a los procedimientos rutinarios, y dado el carácter retrospectivo, no se recabó el consentimiento informado del paciente para el análisis de los resultados. Todos los registros se anonimizaron con un número de muestra y se agregaron por distritos sanitarios y municipios para evitar la identificación de los pacientes. El estudio fue previamente aprobado por el Comité Ético Provincial con fecha 21 de diciembre de 2020 y código interno 1671-N-20.

RESULTADOS

Se seleccionaron 68.587 casos (96,3% de los urocultivos registrados en el Servicio de Microbiología durante el periodo de estudio), de los cuales 57.741 procedieron de adultos y 10.846 de niños. La mediana de edad en los adultos fue de 63,0 [46,0-78,0] años y de los niños de 0,8 [0,1-4,0] años. El 53,7% de los adultos fueron mujeres y el 59,2% niñas. La procedencia de las muestras fue hospitalaria en el 51,1% de los casos, tanto en adultos como en niños; el 13,9% de las muestras de orina en pacientes adultos se obtuvieron a partir de sondajes provisionales, siendo el doble en edades infantiles.

La tasa de incidencia poblacional de BS en adultos fue de 16,6 casos por 1.000 habitantes/año (18,9 casos en mujeres y 14,1 casos en hombres). Estas tasas ascendieron a 77,7 casos por 1.000 habitantes/año en el grupo de 85 a 89 años, de forma más acusada en hombres (88,9 casos) (figura 1). Los menores de 14 años tuvieron una tasa global de BS de 15,6 casos por cada 1.000 habitantes/año, llegando, en los menores de un año, a 196,0 casos en niñas y a 240,2 en niños (figura 1). Las tasas de incidencia mostraron una tendencia decreciente en los años estudiados, tanto en población infantil como adulta, con cifras de 18,2 casos/1.000 habitantes en 2016 y 14,6 casos/1.000 habitantes en 2020 en adultos, y 21,1 y 8,4 casos/1.000 habitantes, en 2016 y 2020 respectivamente, en el caso de menores (figura 2).

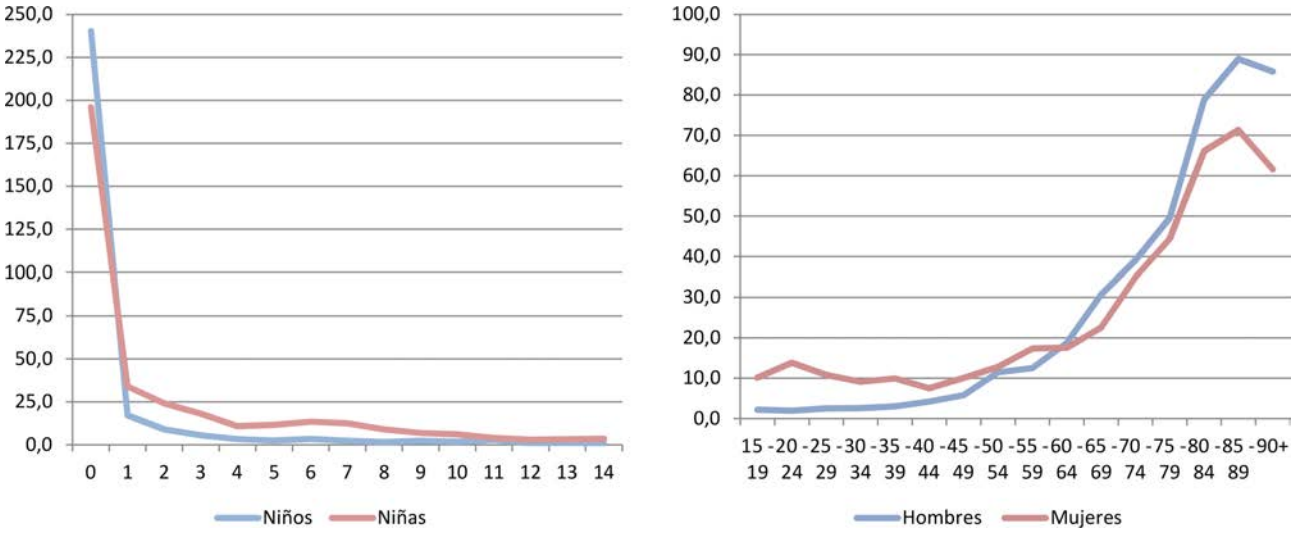

Figura 1 | **Tasas de bacteriuria significativa por 1.000 habitantes según grupos de edad y sexo en niños (izquierda) y adultos (derecha).**

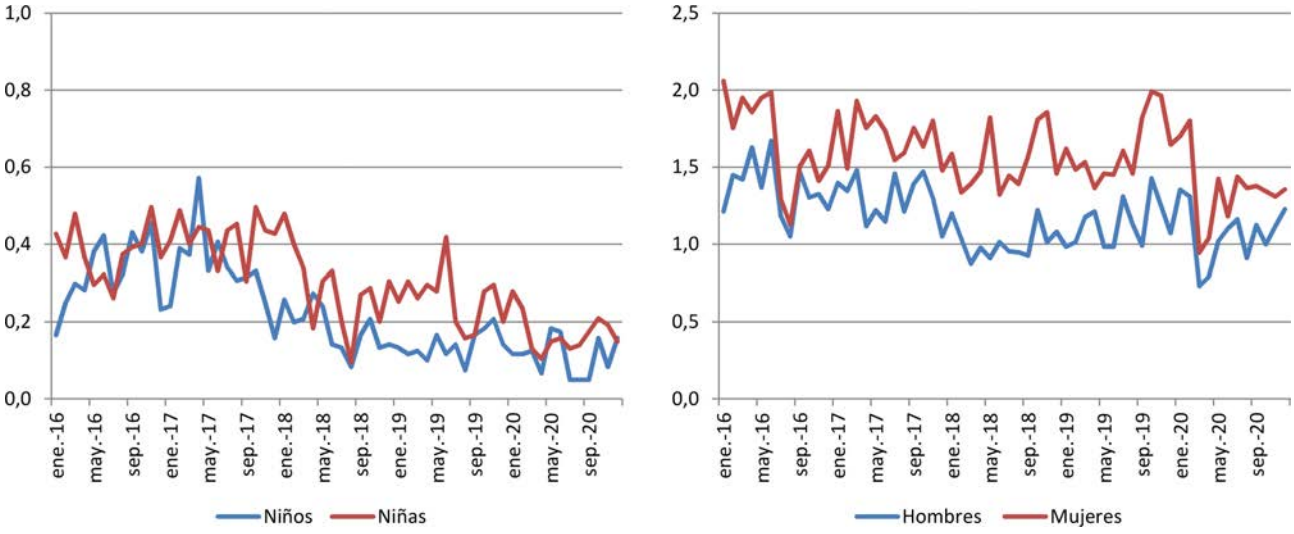

Figura 2 | **Evolución de la incidencia de bacteriuria significativa por 1.000 habitantes entre 2016 y 2020 en población infantil (izquierda) y adultos (derecha).**

El porcentaje de urocultivos positivos en adultos fue del 40,8%, (IC95%: 40,4%-41,2%), asociándose de forma significativa al año (el porcentaje fue superior en los años 2016 y 2017 respecto a 2020; p<0,001), estación del año (un 10% más en otoño respecto a primavera; p<0,001), edad en años (OR=1,01; IC95%: 1,01-1,02; p<0,001), sexo (más frecuente en mujeres, OR=1,50; IC95%: 1,24-1,44; p<0,001), distrito sanitario de adscripción (Nordeste y Sur con un 19% y 14% menos de riesgo, respectivamente, respecto a Granada capital; p<0,001) y sonda permanente respecto a sondaje provisional (OR=1,37; IC95%: 1,28-1,47; p<0,001). No se observó asociación significativa con la procedencia de la muestra ni la zona de residencia (Tabla 1).

En edades infantiles (Tabla 1), el porcentaje de urocultivos positivos fue de 33,8%, (IC95%: 32,9%-34,7%), con asociación significativa con el año (menor frecuencia en 2020 respecto a 2016-2017; p<0,001), estación del año (18% más de riesgo en otoño frente a verano y un 13% más en otoño respecto a invierno; p<0,01), edad (4% menos de riesgo de BS por cada año cumplido; p<0,001), sexo (más frecuente en niñas, OR=1,15;

Tabla 1 **Variables relacionadas con la presencia de bacteriuria significativa en adultos y niños.**

Adultos	Negativo (n=34.210)	Positivo (n=23.531)	OR (IC 95%)	p
Año				<0,001
2016	7.318 (21,4)	5.170 (22,0)	1,08 (1,03-1,15)	
2017	6.964 (20,4)	5.132 (21,8)	1,14 (1,08-1,20)	
2018	6.480 (18,9)	4.376 (18,6)	1,04 (0,99-1,10)	
2019	7.058 (20,6)	4.704 (20,0)	1,03 (0,97-1,08)	
2020	6.390 (18,7)	4.149 (17,6)	1	
Estación del año				<0,001
Invierno	8.777 (25,7)	6.053 (25,7)	0,96 (0,92-1,01)	
Primavera	8.963 (26,2)	5.821 (24,7)	0,91 (0,87-0,95)	
Verano	8.047 (23,5)	5.630 (23,9)	0,98 (0,93-1,03)	
Otoño	8.423 (24,6)	6.027 (25,6)	1	
Edad (años)	58,6 ± 20,8	63, 8± 20,3	1,01 (1,01-1,02)	<0,001
Sexo (mujer)	16.978 (49,6)	14.009 (59,5)	1,50 (1,44-1,54)	<0,001
Tipo de muestra				<0,001
Sondaje provisional	4.282 (12,5)	3.754 (16,0)	1	
Sonda permanente	2.399 (7,0)	2.882 (12,2)	1,37 (1,28-1,47)	
Otros	27.529 (80,5)	16.895 (71,8)	0,70 (0,67-0,73)	
Distrito				<0,001
Granada	12.125 (35,4)	8.458 (35,9)	1	
Metropolitano	15.117 (44,2)	10.597 (45,0)	1,01 (0,97-1,04)	
Nordeste	2.092 (6,1)	1.287 (5,5)	0,88 (0,82-0,95)	
Sur	1.231 (3,6)	719 (3,1)	0,84 (0,76-0,92)	
Resto Andalucía	3.015 (8,8)	2.069 (8,8)	0,98 (0,92-1,05)	
Desconocido	630 (1,8)	401 (1,7)	0,91 (0,80-1,04)	
Niños	**Negativo (n=7.183)**	**Positivo (n=3.663)**	**OR (IC 95%)**	**p**
Año				<0,01
2016	2.115 (29,4)	992 (27,1)	1.05 (0,92-1,21)	
2017	2.031 (28,3)	1.065 (29,1)	1,18 (1,02-1,35)	
2018	1.127 (15,7)	653 (17,8)	1,30 (1,12-1,52)	
2019	1.023 (14,2)	558 (15,2)	1,23 (1,05-1,43)	
2020	887 (12,3)	395 (10,8)	1	
Estación del año				<0,01
Invierno	2.023 (28,2)	978 (26,7)	0,88 (0,79-0,99)	
Primavera	1.779 (24,8)	972 (26,5)	0,99 (0,89-1,11)	
Verano	1.681 (23,4)	781 (21,3)	0,85 (0,75-0,95)	
Otoño	1.700 (23,7)	932 (25,4)	1	
Edad (años)	2,8±3,8	2,3±3,4	0,96 (0,95-0,97)	<0,001
Sexo (mujer)	4.338 (60,4)	2.085 (56,9)	1,15 (1,07-1,25)	<0,01
Procedencia (hospital)	3.563 (49,6)	1.985 (54,2)	1,20 (1,11-1,30)	<0,001
Tipo de muestra				<0,001
Sondaje provisional	1.766 (24,6)	1.172 (32,0)	1	
Sonda permanente	499 (6,9)	76 (2,1)	0,23 (0,18-0,30)	
Otros	4.918 (68,5)	2.415 (65,9)	0,74 (0,68-0,81)	
Distrito				<0,001
Granada	2.058 (28,7)	1.193 (32,6)	1	
Metropolitano	3.983 (5,5)	2.018 (55,1)	0,87 (0,80-0,96)	
Nordeste	159 (2,2)	58 (1,6)	0,63 (0,46-0,86)	
Sur	347 (4,8)	122 (3,3)	0,61 (0,49-0,75)	
Resto	369 (5,1)	146 (4,0)	0,68 (0,56-0,83)	
Desconocido	267 (3,7)	126 (3,4)	0,81 (0,65-1,02)	
Ruralidad				<0,01
Rural	365 (5,1)	142 (3,9)	1	
Semirural	1.758 (24,5)	839 (22,9)	1,23 (0,99-1,51)	
Urbano	4.793 (66,7)	2.556 (69,8)	1,37 (1,12-1,67)	
Desconocido	267 (3,7)	126 (3,4)	1,21 (0,91-1,61)	

Valores expresados como frecuencia (porcentaje) y media ± desviación típica

IC95%: 1,07-1,25; p<0,01), procedencia hospitalaria (OR=1,20; IC95%: 1,11-1,30; p<0,001), 4,37 veces más muestras positivas obtenidas por sondaje provisional respecto a sondaje permanente y un 35% más respecto a otro tipo de muestras (p<0,001), y mayor frecuencia en el distrito sanitario Granada respecto a los restantes (p<0,001). La positividad del urocultivo fue significativamente más frecuente en el ámbito urbano respecto al ámbito rural (OR=1,37; IC95%: 1,12-1,67; p<0,01).

Considerando solo los urocultivos con resultado positivo, en las muestras procedentes de adultos se aisló un porcentaje superior de bacilos gramnegativos en mujeres (62,0%, p<0,001) y una mayor frecuencia de levaduras en pacientes con sonda permanente (25,4%, p<0,001) y en pacientes de mayor edad (70,8±17,7; p<0,001). Respecto a las estaciones del año, las levaduras y los cocos grampositivos aparecieron con mayor frecuencia en invierno (p<0,01). En el grupo de niños el comportamiento fue similar al de adultos, también con resultados significativos para el sexo, el tipo de muestra, estación del año (frecuencia mayor en otoño de levaduras) y la edad. En los adultos se aislaron bacilos gramnegativos más frecuentemente en el ámbito urbano que en el rural (p<0,001), mientras que en niños no hubo evidencias de tal asociación (Tabla 2).

Del total de urocultivos, 23.565 realizados en adultos (40,7%) y 3.542 (32,7%) en niños se asociaron a un episodio de ingreso hospitalario. En estos registros se analizaron los factores de riesgo asociados, encontrándose en el análisis bivariante asociaciones significativas en adultos entre urocultivos positivos y la edad (OR=1,02; IC95%: 1,01-1,02; p<0,001), mujer (OR=1,34; IC95%: 1,27-1,41; p<0,001), ingreso urgente (OR=1,10; IC95%: 1,01-1,19; p<0,05), hipertensión arterial (OR=1,13; IC95%: 1,07-1,20; p<0,001), diabetes tipo II (OR=1,21 IC95%: 1,14-1,30; p<0,001), hiperlipemia (OR=1,30;IC95%: 1,05-1,22; p<0,01), obesidad (OR=1,27; IC95%: 1,17-1,38; p<0,001), enfermedad renal (OR=1,29; IC95%: 1,21-1,38; p<0,001) e insuficiencia cardiaca (OR=1,40; IC95%:

Tabla 2 **Variables relacionadas con el tipo de microorganismo aislado en urocultivos positivos**

Adultos	Bacilos gramnegativos (n=14.124)	Cocos grampositivos (n=5.218)	Levaduras (n=1.416)	Otros (n=2.771)	p
Sexo (Mujer)	8.750 (62,0)	2933 (56,2)	738 (52,1)	1587 (57,3)	<0,001
Procedencia (Hospital)	7.134 (50,5)	2738 (52,5)	587 (41,5)	1639 (59,1)	<0,001
Tipo de muestra					<0,001
Sondaje provisional	2.102 (14,9)	782 (15,0)	436 (30,8)	434 (15,7)	
Sonda permanente	1.491 (10,6)	614 (11,8)	359 (25,4)	418 (15,1)	
Otros	10.531 (74,6)	3822 (73,2)	621 (43,9)	1919 (69,3)	
Distrito Sanitario					<0,001
Granada	5.237 (37,1)	1823 (34,9)	419 (29,6)	979 (35,3)	
Metropolitano	6.268 (44,4)	2351 (45,1)	680 (48,0)	1298 (46,8)	
Nordeste	696 (4,9)	313 (6,0)	135 (9,5)	143 (5,2)	
Sur	420 (3,0)	182 (3,5)	42 (3,0)	75 (2,7)	
Resto	1.246 (8,8)	449 (8,6)	124 (8,8)	249 (9,0)	
Desconocido	257 (1,8)	10 (1,9)	16 (1,1)	27 (1,0)	
Edad	62,9 ± 20,7	63,0 ± 20,3	70,8 ± 17,7	65,7 ± 19,1	<0,001
Ruralidad					<0,001
Rural	984 (7,0)	419 (8,0)	125 (8,8)	199 (7,2)	
Semirural	2.975 (21,1)	1.169 (22,4)	344 (24,3)	633 (22,8)	
Urbano	9.908 (70,2)	3.530 (67,7)	931 (65,7)	1.912 (69,0)	
Desconocido	257 (1,8)	100 (1,9)	16 (1,1)	27 (1,0)	
Niños	Bacilos gramnegativos (n=2.316)	Cocos grampositivos (n=792)	Levaduras (n=30)	Otros (n=520)	p
Sexo (Mujer)	1.423 (61,4)	389 (49,1)	16 (53 3)	255 (49,0)	<0,001
Procedencia (Hospital)	1.273 (55,0)	410 (51,8)	20 (66,7)	279 (53 7)	0,224
Tipo de muestra					<0,05
Sondaje provisional	779 (33,6)	222 (28,0)	9 (30,0)	160 (30,8)	
Sonda permanente	52 (2,2)	15 (1,9)	2 (6,7)	7 (1,3)	
Otros	1.485 (64,1)	555 (70,1)	19 (63,3)	353 (67,9)	
Distrito Sanitario					0,143
Granada	768 (33,2)	248 (31,3)	7 (23,3)	169 (32 5)	
Metropolitano	1.279 (55,2)	442 (55,8)	14 (46,7)	281 (54,0)	
Nordeste	31 (1,3)	18 (2,3)	1 (3,3)	8 (1,5)	
Sur	66 (2,8)	29 (3,7)	4 (13,3)	23 (4,4)	
Resto	90 (3,9)	32 (4,0)	2 (6,7)	21 (4,0)	
Desconocido	82 (3,5)	23 (2,9)	2 (6,7)	18 (3,5)	
Edad	2,8 ± 3,6	1,4 ± 2,7	2,2 ± 4,1	1,2 ± 2,5	<0,001
Ruralidad					0,416
Rural	91 (3,9)	32 (4,0)	1 (3,3)	18 (3,5)	
Semirural	519 (22,4)	205 (25,9)	9 (30,0)	106 (20,4)	
Urbano	1.624 (70,1)	532 (67,2)	18 (60,0)	378 (72,7)	
Desconocido	82 (3,5)	23 (2,9)	2 (6,7)	18 (3,5)	

Valores expresados como frecuencia (porcentaje) y media ± desviación típica

1,30-1,50; p<0,001), sin significación para EPOC ni diagnóstico de COVID-19. Se encontró una relación inversa con la dependencia de nicotina (OR=0,73; IC95%: 0,65-0,81; p<0,001), neoplasia maligna (OR=0,82; IC95%: 0,77-0,88; p<0,001) y neumonía (OR=0,79; IC:95% 0,66-0,94; p<0,01) (Tabla 3). En el análisis multivariante, por cada año de edad transcurrido el riesgo de BS aumentó un 2%, (OR=1,02; IC95%: 1,01-1,02), con un riesgo 36% mayor en mujeres

Tabla 3 **Factores de riesgo relacionados con la bacteriuria significativa en adultos ingresados**

Variable	Negativo (n=13.993)	Positivo (n=9.532)	OR bivariante (IC 95%)	OR multivariante (IC95%)
Edad	63,9 ± 19,4	69,5 ± 17,0	1,02 (1,01-1,02)	1,02 (1,01-1,02)
Sexo (mujer)	5.076 (53,3)	6435 (46,0)	1,34 (1,27-1,41)	1,36 (1,29-1,43)
Tipo ingreso (urgente)	8.517 (89,4)	12.375 (88,4)	1,10 (1,01-1,19)	
Hipertensión	4.334 (31,0)	3.204 (33,6)	1,13 (1,07-1,20)	
Diabetes tipo II	2.407 (17,2)	1.919 (20,1)	1,21 (1,14-1,30)	
Hiperlipemia	1.844 (13,2)	1.393 (14,6)	1,30 (1,05-1,22)	
Tabaco	1.082 (7,7)	546 (5,7)	0.73 (0,65-0,81)	
Obesidad	1.299 (9,3)	1.097 (11,5)	1,27 (1,17-1,38)	1,18 (1,08-1,29)
Enfermedad renal	2.539 (18,1)	2.124 (22,3)	1,29 (1,21-1,38)	1,17 (1,10-1,26)
EPOC	867 (6,2)	591 (6,2)	1,00 (0,90-1,12)	
Neoplasia	2.913 (20,8)	1.689 (17,7)	0,82 (0,77-0,88)	0,88 (0,82-0,94)
Insuficiencia cardíaca	1.901 (13,6)	1.715 (18,0)	1,40 (1,30-1,50)	
Neumonía	364 (2,6)	196 (2,1)	0,79 (0,66-0,94)	0,76 (0,63-0,90)
COVID-19*	299 (9,9)	171 (8,6)	0,86 (0,71-1,05)	

***Solo para el año 2020**

Tabla 4 **Correlación de Pearson entre el porcentaje de bacteriurias significativas por municipio y variables sociodemográficas asociadas (n=414)**

Variable	Altitud	Distancia al hospital	Tasa de extranjería	Tasa de natalidad	Tasa de mortalidad	Tasa de paro	Renta media anual
Correlación	-0,007	0,037	-0,009	-0,039	0,068	-0,060	-0,037
p	0,891	0,449	0,854	0,429	0,169	0,223	0,453

(OR=1,36; IC95%: 1,29-1,43), un 18% superior en obesos (OR=1,18; IC95%: 1,08-1,29), un 17% más frecuente en pacientes con enfermedad renal (OR=1,17; IC95%: 1,10-1,26), un 14% menos de riesgo en pacientes con neoplasia (OR=0,88; IC95%: 0,82-0,94) y un 32% menos en pacientes con neumonía (OR=0,76; IC95%: 0,63-0,90), todas ellas de forma significativa (p<0,01). En niños solo se encontraron relaciones significativas del urocultivo positivo con la edad, con un 10% menos de riesgo por cada año cumplido (OR=0,91; IC95%: 0,89-0,93; p<0,001), neoplasia maligna (OR=0,53; IC95%: 0,38-0,73; p<0,001) y con la presencia de neumonía (OR=0,06; IC95%: 0,01-0,43; p<0,001). La mediana de días de estancia hospitalaria en adultos con urocultivo positivo fue significativamente superior respecto a adultos con urocultivos negativos (16 días vs 12 días, p<0,001), siendo igualmente significativa en niños (9 días en urocultivos negativos vs 7 días en BS positivo, p<0,001).

Se aislaron bacilos gramnegativos en el 60,0% de los urocultivos obtenidos de adultos y en el 63,3% de los niños. El microorganismo más frecuentemente aislado fue *E. coli*, tanto en adultos (34,4%) como en niños (47,3%), seguido de *Enterococcus faecalis*, con un 14,0% y 18,3% para cada grupo poblacional, respectivamente. Tanto en población adulta como en población infantil, en el 14,4% de los urocultivos se aislaron dos microorganismos.

En la relación de los factores de riesgo según grupo de bacterias, en el 35,1% de los urocultivos en los que se aisló un gramnegativo, el paciente presentó hipertensión arterial y en el 19,6% de aislamientos de grampositivos presentaron neoplasia. En el 34,6%, 21,4%, 6,03% y 4,7% de los aislamientos de levaduras los pacientes presentaron enfermedad renal, insuficiencia cardíaca, neumonía y presencia de COVID-19, respectivamente. En niños, en el 8,3% de los aislamientos de levaduras hubo enfermedad renal asociada, significativamente superior a otros tipos de microorganismos (p<0,01).

A nivel de municipios, no se encontraron correlaciones significativas entre el porcentaje de urocultivos positivos y las variables sociodemográficas analizadas (Tabla 4).

DISCUSIÓN

En este estudio se analizó una importante muestra de adultos y niños del sur de España con BS, procedentes tanto de consultas externas y urgencias como de hospitalización. Se ha evidenciado una mayor frecuencia de urocultivos positivos en el sexo femenino, la edad avanzada y los niños menores de un año, el sondaje permanente, residir en zonas urbanas, últimos meses del año (coincidiendo con el periodo otoñal) y durante los años 2016 y 2017. A diferencia de lo obtenido por Palacios [7], que observan un incremento en los casos de BS en los últimos 18 años, en nuestro estudio se observa una disminución durante los años analizados, con un porcentaje de urocultivos positivos menor en 2020 respecto a los años anteriores, sobre todo en niños, posiblemente debido a que durante la pandemia por COVID-19 la asistencia al hospital por parte de los usuarios fue mucho menor por miedo al contagio, unido a que la actividad habitual tuvo que reducirse para atender a pacientes con dicha patología. Además, cabe destacar que a principio de 2018 se produjo un cambio organizativo en la gestión del hospital que derivó en una disminución de los urocultivos y, por tanto, en un descenso de los diagnósticos positivos de BS, por lo que, unido a lo comentado anteriormente sobre la pandemia, el descenso fue patente durante los cinco años.

La incidencia de BS en menores obtenida en el presente estudio fue inferior a la encontrada en otros trabajos [12] (15,6 vs 19,0, respectivamente). El estudio citado se llevó a cabo en Holanda, con condiciones climáticas diferentes a las de la provincia de Granada. Hay que destacar también que aunque el servicio de Microbiología es referente del Área Hospitalaria Virgen de las Nieves, recibe muestras en menor proporción de otras procedencias hospitalarias y comunitarias, por lo que la incidencia resultante podría estar sobrestimada.

Respecto a la frecuencia de BS en mujeres, igualmente, en el presente estudio, observamos tasas inferiores a las encontradas en otro trabajo realizado en Francia (18,9 vs 24,0, respectivamente) [19]. Aunque las BS se dan en mayor porcentaje en mujeres que en hombres, al calcular la incidencia poblacional por grupos de edad y sexo obtenemos cifras superiores en hombres a partir de los 60 años, debido a que la población masculina en estos grupos de edad desciende con respecto a la población femenina. A diferencia de lo encontrado por Redondo [20] se encontró un descenso significativo en la incidencia de urocultivos positivos a lo largo del periodo de estudio, teniendo en cuenta que los periodos de estudio en ambas investigaciones son diferentes (2000-2015 en el trabajo de Redondo vs 2016-2020 en el presente trabajo).

Respecto a las características sociodemográficas de las BS, hemos encontrado resultados diferentes a las descritas por otros autores como Lusignan [21] y Kwok [22], que observaron más casos de infecciones en zonas rurales y/o con menos de 30.000 habitantes. En general, se puede asumir que la población que reside en zonas urbanas está expuesta a mayores niveles de contaminación, lo que puede causar mayor número de ingresos hospitalarios por neumonía e ITU [22]. Además, hay que considerar que la falta de un acceso más rápido y directo a los servicios sanitarios puede generar un infrarregistro de pacientes procedentes de zonas rurales. No obstante, se necesitarían estudios más profundos para corroborar estos resultados.

Atendiendo a los factores de riesgo en pacientes hospitalizados, no hemos podido evidenciar relación entre la BS y la enfermedad pulmonar obstructiva crónica, como De Miguel [23], aunque sí se ha observado relación con factores descritos en la literatura como hipertensión, diabetes tipo II, obesidad, enfermedad renal, e insuficiencia cardiaca [24]. El presente estudio revela además relación bivariante entre la hiperlipemia y las BS, al igual que Delgado [25] y Canturk [26], que encontraron esta misma asociación en pacientes quirúrgicos. Los pacientes con hiperlipemia suelen tener otros factores de riesgo asociados que pueden predisponer a la adquisición de infecciones hospitalarias [26]. En el actual trabajo, la asociación negativa encontrada entre la presencia de neoplasias o neumonía y BS puede ser debida a no haber analizado otras variables confusoras que pudieran intervenir en dicha relación, como el tipo de tratamiento administrado o la duración de este.

Respecto a la relación entre BS y diagnóstico de COVID-19 en pacientes ingresados, la cifra de infección nosocomial por BS en pacientes COVID-19 fue del 21,5% [27]; sin embargo, en el estudio de Ong [28], encontraron mayor proporción de BS en pacientes no COVID-19 ingresados en UCI, siendo la presencia de una sonda permanente el factor de riesgo más importante de BS en esta situación. En el trabajo actual también se aprecia una mayor proporción de BS en pacientes no COVID-19, aunque sin resultados significativos. La pandemia ha conllevado un refuerzo de las medidas de prevención y control de la infección en los hospitales en todos los ámbitos de la atención sanitaria y no solamente en pacientes COVID-19, por lo que cabe esperar que el desarrollo de BS nosocomiales sea similar en ambos grupos de pacientes. En lo que respecta a los días de estancia, en el estudio de Lagoe [29] se constata que los pacientes ingresados con BS tienen significativamente entre 9 y 12 días más de estancia que los que tienen urocultivos negativos, estando dicha diferencia en nuestro estudio en un rango menor, entre 6 y 8 días. El estudio citado está realizado en la ciudad de Nueva York, con un sistema sanitario muy diferente al español, por lo que la gestión de pacientes puede variar considerablemente entre los dos países.

En cuanto al tipo de microorganismo aislado, *E. coli* es el más frecuente en cualquier población, sin distinción de edad [6]. Respecto a la casuística de BS según los meses del año, nuestro estudio muestra la época otoñal como la de mayor frecuencia de BS en adultos. Este resultado es opuesto a los encontrados en la literatura, que revelan una mayor incidencia de infección nosocomial, en general, en la época estival [30], así como de BS, en particular, en la misma época del año [31]. La estructura colonizadora de *E. coli* facilita una mayor adherencia y rápida invasión de las vías urinarias [32], produciéndose en su mayoría, en nuestro caso, en los meses con tendencia al frío.

Este estudio presenta algunas limitaciones. La fuente de información utilizada ha sido la base de datos de urocultivos del laboratorio de microbiología, que recoge información li-

mitada sobre las características clínicas y demográficas de los pacientes. Ello se ha podido suplir, en parte, con el estudio realizado de los urocultivos en pacientes ingresados, donde al cruzar con el Conjunto Mínimo Básico de datos que, aunque al ser una base de datos administrativa también presenta sus limitaciones, es útil para la determinación de factores de riesgo presentes al ingreso, que de otra forma no podrían obtenerse salvo con entrevistas a los propios pacientes y/o acceso individual a la historia de salud digital. Los factores de riesgo en pacientes no ingresados son más difíciles de obtener en nuestro centro, pues no existe un registro sistematizado de enfermedades asociadas a los pacientes que acuden a consultas externas y a urgencias, requiriendo de procedimientos complejos de extracción de texto de dichos episodios.

Otra de las limitaciones que se presentan es que el resultado de los urocultivos puede verse alterado en función de ciertos tratamientos que estén recibiendo los pacientes, información que no consta en las bases de datos analizadas. Al ser un estudio basado en toda la casuística de urocultivos, están incluidos tanto los pacientes que reciben tratamiento como los que no, sin posibilidad de identificar el tratamiento administrado y la duración del mismo en aquellos que lo tienen pautado.

Como fortaleza cabe destacar que es un estudio realizado en una amplia serie de casos de cinco años en la que se han analizado, tanto en adultos como en niños, no solo características clínicas, sino también sociodemográficas, geográficas y temporales. La falta de correlación existente entre el porcentaje de BS y las variables sociodemográficas concluye que hay independencia entre la distribución de estas infecciones y las características de los municipios analizados, por lo que las posibles diferencias entre zonas rurales y urbanas pueden ser achacables a factores no analizados en este estudio.

En conclusión, las BS observadas en niños y adultos en nuestra zona de estudio tienen características similares a las encontradas en otras áreas geográficas a nivel mundial, salvo que hemos observado una tendencia decreciente en el tiempo en la incidencia de BS en los años estudiados. Durante el estado de pandemia, no se ha encontrado relación entre las BS y el diagnóstico de COVID-19 en pacientes hospitalizados. La frecuencia de BS en niños disminuye en ámbitos rurales frente a los urbanos, no estando asociadas a las características sociodemográficas de los municipios de residencia.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Impact of one year of pandemic on Spanish Intensive Care Units

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ABSTRACT

Objective. To measure the impact of the pandemic in Spanish ICUs.

Material and methods. On-line survey, conducted in April 2021, among SEMICYUC members. Participants were asked about number of patients admitted, increase in the number of beds and staff, structures created in the hospital and self-assessment of the work performed.

Results. We received 246 answers from 157 hospitals. 67.7% of the ICUs were expanded during the pandemic, overall increase in beds of 58.6%. The ICU medical staff increased by 6.1% and there has been a nursing shortage in 93.7% of units. Patients exceeded 200% the pre-pandemic ICU capacity. In 88% of the hospitals the collaboration of other specialists was necessary. The predominant collaboration model consisted of the intensive care medicine specialist being responsible for triage and coordinating patient management. Despite that 53.2% centres offered training for critical care, a deterioration in the quality of care was perceived. 84.2% hospitals drew up a Contingency Plan and in 77.8% of the hospitals a multidisciplinary committee was set up to agree on decision-making.

Self-evaluation of the work performed was outstanding and 91.9% felt proud of what they had achieved, however, up to 15% considered leaving their job.

Conclusions. The Spanish ICUs assumed an unprecedented increase in the number of patients. They achieved it without hardly increasing their staff and, while intensive care medicine training was carried out for other specialists who collaborated. The degree of job satisfaction was consistent with pre-pandemic levels.

Keywords: COVID-19, SARS-CoV-2, pandemic, ICU, Spain

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Impacto de un año de pandemia en las Unidades de Cuidados Intensivos de España

RESUMEN

Objetivo. Medir el impacto de la pandemia COVID-19 en las UCI españolas.

Material y métodos. Cuestionario online, realizado en abril 2021 entre socios de SEMICYUC. Se interrogó acerca del número de pacientes ingresados, incremento en número de camas y personal, estructuras creadas en el hospital y autoevaluación del trabajo realizado.

Resultados. Recibimos 246 respuestas de 157 hospitales. El 67.7% de las UCI se expandieron durante la pandemia, con un incremento de camas del 58.6%. El personal médico de las UCI aumentó un 6.1% y hubo escasez de enfermería en el 93.7% de las unidades. Los pacientes excedieron un 200% la capacidad pre-pandemia y en el 88% de los hospitales fue necesaria la colaboración de otros especialistas, siendo el modelo predominante aquel en que el especialista en medicina intensiva era responsable del triaje y coordinaba el tratamiento del paciente. A pesar de que en el 53.2% de los centros se ofreció formación en medicina intensiva se detectó un deterioro de la calidad asistencial. El 84.2% de los hospitales elaboraron un plan de contingencia y el 77.8% conformaron un comité multidisciplinar para consensuar decisiones. La evaluación del trabajo fue sobresaliente y el 91.9% se siente orgulloso del resultado, pero hasta el 15% consideró abandonar la especialidad.

Conclusiones. Las UCI españolas asumieron un incremento de pacientes sin precedentes, sin apenas aumento del personal y mientras formaban a otros especialistas que colaboraron. El grado de satisfacción con el trabajo realizado fue similar al pre-pandemia.

Palabras clave: COVID-19, SARS-CoV-2, pandemia, UCI, España

BACKGROUND

Coronavirus disease 2019 (COVID-19) has meant a challenge for global healthcare systems. By 28 October 2021 over 240 million cases and approximately 5 million deaths have been declared [1]. The most severe cases, admitted to Intensive Care Units (ICU), exceeded their capacity all over the world, including Spain [2–7]. A relationship was established between the difficulty in accessing an ICU bed, or ICU admission during periods of overload, and a higher risk of death [8,9].

The pandemic has generated a heavy overload for ICU medical staff, both as individual [10] (professionals suffered from significant work and emotional overload, together with the scientific uncertainty of treating a previously unknown disease), as a group (each unit drew up its own organizational response to maximize available resources), and also in institutional terms: the *Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias* (SEMICYUC) and its working groups drew up various documents [11–20] and organized different training activities for their dissemination.

Our objective is to find out how the Spanish ICUs adapted during the first year of the pandemic and to quantify the acquisition of new equipment and the incorporation of other health professionals; in addition, we try to explore and document the feelings of the ICU medical staff.

METHODS

The SEMICYUC Planning, Organization and Management Working Group and the Infectious Diseases and Sepsis Working Group developed a 113-question questionnaire that includes the following sections: 1: participant data and site baseline general data, 2: material and human resources available before and during the pandemic, 3: transversal structures created in the hospital, 4: organization and care load before and during the pandemic, 5: subjective perception of the impact of the pandemic on the role and visibility of Intensive Care Medicine, 6: impact of the pandemic on non-care activity (education, investigation...) and evaluation of activities and documents. January 2020 and February 2021 were considered as pre-pandemic and post-pandemic references, respectively. The questionnaire used can be consulted [21].

The project was approved by the Managing Board of SEMICYUC and sent to partners by e-mail. The survey period was from 15th to April 20th 2021. Responses were voluntary and anonymous. No personal data was recorded although data on job post and unit were requested. Ethics committee approval was not considered necessary because of the type of study. The survey was voluntary, not remunerated and consent to use the data obtained was deemed implicit for taking part. For the analysis, hospitals were classified as under 200 beds, 200-500 beds and more than 500 beds.

For sections 2, 3 and 4 we analysed one response per hospital. In the event of receiving more than one answer per site, we selected the answer according to a hierarchical order (head of department, clinical chief, specialist, fellow). For the remaining sections, data is shown in aggregate form.

Percentage increases (for beds, closed boxes, negative pressure boxes, staff and guard number) were calculated using the following formula:

Percentage increase (increase %) *variable X*=(*variable X* February 2021-*variable X* January 2020)/*variable X* January 2020 x 100.

Results are shown as absolute value and percentage, and as median and p25 and p75 for qualitative and quantitative variables, respectively. Answers were analysed according to hospital size. Qualitative and quantitative variables were compared using the statistical Chi2 and Kruskall-Wallis tests, respectively. Statistically significant differences were deemed those with $p<0.05$.

RESULTS

We received 246 answers from 157 hospitals, representing the 17 autonomous communities in which Spain is administratively distributed (Additional File 1). Of the total SEMICYUC partners who responded, 58 (23.6%) were heads of department, 15 (6.1%) clinical chief, 128 (50.4%) specialists 12 (4.9%) fellows. The median experience in the ICU was 18 (9, 25) years. A total of 108 (68.4%) of the analyzed hospitals offered training in Intensive Care Medicine.

Material and human resources available during the pandemic (Table 1). Capacity was increased in 67.7% of Spanish ICUs with an increase of 9 (4, 18) beds, which represents 58.6% compared to the number of pre-pandemic beds. The number of ICU medical staff increased by 6.1% (there was no increase in small and medium-sized hospitals, however, there was an increase of 10.6% in hospitals with more than 500 beds, $p=0.014$).

In 119 (75.3%) units there was at least one doctor infected with SARS-CoV-2: in 7 (46.7%) ICU from hospitals with <200 beds, 62 (76.5%) from hospitals with 200-500 beds and 50 (80.6%) from hospitals >500 beds ($p=0.022$).

On the date of completing the survey, 229 (93.1%) of respondents had received at least one dose of the vaccine.

Transversal structures created in the hospital (Table 2). Only 15.8% of hospitals did not design a Contingency Plan and 29.1% did not have a de-escalation plan. A COVID committee was created in 77.8% of the hospitals.

Treatment organization and work overload (Table 3). Collaboration with other specialists was necessary in 88% of the hospitals due to the excessive number of patients, that exceeded 200% of ICU pre-pandemic capacity.

The negative impact of the pandemic on the assistance quality, marked on a scale from 0 to 10, was evaluated as 8 (7, 10) but only 19 (12%) units used quality indicators to measure this issue. Using the same scale, concern over higher than usual mortality was graded as 9 (7, 10). Concern over insufficient individual protection equipment (IPE) during the first wave

Table 1 **Human and material resources.**

	Overall	Hospital size			P
		<200 beds	200- 500 beds	>500 beds	
Number of hospitals	157	15 (9.6)	80 (51.0)	62 (39.5)	
Beds per unit in January 2020	16 (10, 27)	6 (6, 8)	12 (10, 16)	30 (21.5, 35)	<0.001
Beds per unit in February 2021	28 (16, 41)	10 (7, 15)	22 (15.25, 30)	42 (34, 55)	<0.001
Beds increase (%)	58.6 (21.4, 108.3)	60 (0, 133.3)	72.1 (30.2, 117.6)	43.7 (20, 96.9)	0,151
Isolation beds 2020	11 (6, 18)	6 (2, 8)	10 (5.3, 13.8)	19 (7.8, 30)	<0.001
Isolation beds 2021	13 (8, 25)	6 (6, 8)	12 (8, 16)	27.5 (12.8, 37)	<0.001
Increase in isolation beds (%)	0 (0, 57.1)	0 (0, 50)	0 (0, 66.7)	16.8 (0, 53.6)	0,469
Pressure negative beds 2020	0 (0, 2)	0 (0, 0)	0 (0, 2)	0 (0, 3)	0,025
Pressure negative beds 2021	1 (0, 6)	0 (0, 0)	2 (0, 7)	2 (0, 6)	0,003
Increase in pressure negative beds (%)	0 (0, 20)	0 (0, 0)	0 (0, 87.5)	0 (0, 0)	0.230
Medical staff in January 2020	11 (8, 16)	6 (5, 8)	9 (7, 12)	17 (14, 22)	
Medical staff in February 2021	11 (9, 18)	6 (5, 8)	10 (8, 12)	19.5 (25.3, 26.8)	
Increase in medical staff (%)	6.1 (0, 20)	0 (0, 0)	0 (0, 20)	10.6 (0, 21.8)	0.014
Guards per physician pre-pandemic	5 (4, 5)	6 (5, 6)	5 (4, 5)	4.5 (4, 5)	0.001
Guards per physician during pandemic	7 (6, 8)	7 (6, 7)	7 (6, 8)	6.3 (6, 7)	0,006
Increase in guards (%)	40 (20, 75)	16.7 (0, 40)	60 (25, 100)	40 (22.5, 56.3)	0,002
Increase in nursing ratio; n (%)	47 (30.1)	3 (20.0)	27 (33.8)	17 (27.9)	0.502
Difficulty in hiring nursing staff; n (%)	148 (93.7)	14 (93.3)	76 (93.8)	58 (93.5)	0,882
Extension of the ICU* performed; n (%)	107 (67.7)	11 (73.3)	56 (69.1)	40 (64.5)	0.742
Extension of the ICU* scheduled; n (%)	72 (45.6)	7 (46.7)	35 (43.2)	30 (48.4)	0.437
Acquisition of material					
HFO; n (%)	150 (94.9)	14 (93.3)	77 (95.1)	59 (95.2)	0.956
NIMV; n (%)	107 (67.7)	7 (46.7)	61 (75.3)	39 (62.9)	0,100
MV; n (%)	149 (94.3)	12 (80.0)	79 (97.5)	58 (93.5)	0.047
ECMO; n (%)	31 (19.6)	0 (0)	5 (6.2)	26 (41.9)	<0.001
ECCO2-R; n (%)	21 (13.3)	1 (6.7)	10 (12.3)	10 (16.1)	0.292
Monitors; n (%)	107 (67.7)	8 (53.3)	55 (67.9)	44 (71.0)	0.502
HD monitoring system; n (%)	57 (36.1)	2 (13.3)	27 (33.3)	28 (45.2)	0.063
Respiratory monitoring system; n (%)	43 (27.2)	1 (6.7)	22 (27.2)	20 (32.3)	0.111
Ultrasound; n (%)	87 (55.1)	8 (53.3)	42 (51.9)	37 (59.7)	0.432
EFT equipment; n (%)	48 (30.4)	7 (46.7)	22 (27.2)	19 (30.6)	0.516

Unless expressed otherwise, results are shown as median and IQR

EFT: extracorporeal filtration techniques; ECMO: extracorporeal membrane oxygenation system, ECCO2-R: system for extracorporeal elimination of CO_2, HD: haemodynamics, HFO: high flow oxygen therapy, IQR: interquartile range, MV: mechanical ventilation, NIMV: non-invasive mechanical ventilation

*Extension of the ICU: permanent extension of the number of ICU beds

was graded as 9 (8, 10) and concern for being infected with SARS-CoV-2 was graded as 9 (8, 10). At the time of completing the survey, these concerns were lower: lack of IPE: 3 (2, 6) and infection: 6 (4, 7).

Subjective perception of the role of Intensive Care Medicine during the pandemic (Table 4). 61.8%, 79.3% and 89.4% of the participants have the feeling that the opinion about the ICU has improved for hospital manager, for oth-

Table 2 Transversal structures created in hospital.

	Overall	Hospital size			P
		<200 beds	200- 500 beds	>500 beds	
Number of hospitals	157	15 (9.6)	80 (51.0)	62 (39.5)	
COVID committee; n (%)	123 (77.8)	9 (60.0)	61 (75.3)	53 (85.5)	0.177
Evaluation COVID committee operation (0-10)	7 (6, 8)	8 (5.75, 9.0)	7 (6, 8)	7 (5, 8)	0.161
Evaluation quality of communication with superiors (0-10)	7 (5, 8)	7 (6, 9)	7 (5, 9)	6 (4, 8)	0.005
Psychological support unit; n (%)	84 (53.2)	6 (40.0)	42 (51.9)	36 (58.1)	0.672
Evaluation psychological support unit tool (0-10)	6 (5, 8)	8 (5.75, 9.25)	6 (5, 8)	6 (3, 8)	0.204
Contingency Plan; n (%)	133 (84.2)	13 (86.7)	67 (82.7)	53 (85.5)	0.959
De-escalation Plan; n (%)	112 (70.9)	11 (73.3)	54 (66.7)	47 (75.8)	0.072

Unless expressed otherwise, results are shown as median and IQR

Table 3 Treatment organization and overload.

	Overall	Hospital size			P
		<200 beds	200- 500 beds	>500 beds	
Maximum admitted patients at the same time	34 (21.2, 48)	15 (9, 19)	29 (20, 38)	47.5 (35, 70)	<0.001
Maximum COVID patients admitted at the same time	28 (17.8, 42)	11 (6.8, 14.3)	24 (16, 35)	40 (26, 60.5)	<0.001
Maximum peak patients/beds January 2020	200 (150, 269.8)	166.7 (100, 262.5)	240.8 (173.5, 291.5)	190.5 (137.4, 229.9)	0.007
Maximum peak COVID patients/beds January 2020	175 (116.6, 239.9)	142.1 (85.9, 212.5)	200.0 (150.0, 250.0)	161.4 (100.0, 208.4)	0.035
Treatment in open cohorts; n (%)	86 (54.4)	6 (40.0)	45 (55.6)	35 (56.5)	0.131
Collaboration from other specialities					
Other specialities; n (%)	139 (88.0)	11 (73.3)	71 (87.7)	57 (91.9)	0.138
Anaesthesiology; n (%)	134 (84.8)	10 (66.7)	68 (85.0)	56 (90.3)	0.005
Cardiology; n (%)	29 (18.4)	0 (0)	12 (14.8)	17 (27.4)	0.025
Paediatrics; n (%)	39 (24.7)	1 (6.7)	14 (17.3)	24 (38.7)	0,006
Emergency Department; n (%)	23 (14.6)	2 (14.6)	12 (14.8)	9 (14.5)	0,924
Pneumology; n (%)	23 (14.6)	1 (6.7)	12 (14.8)	10 (16.1)	0.698
Mode of collaboration					
Coordination (triage and care) by ICU; n (%)	87 (60.0)	9 (75.0)	45 (60.0)	33 (56.9)	0,507
Triage by ICU; n (%)	43 (29.7)	3 (25)	22 (29.3)	18 (31.0)	0.913
Independent management; n (%)	15 (10.3)	0 (0)	8 (10.7)	7 (12.1)	0,454
Critical patient care training					
Programme based on SPACE-19; n (%)	25 (15.8)	0 (0)	14 (17.3)	11 (17.7)	0.192
Local training programme; n (%)	56 (35.4)	9 (60.0)	25 (30.9)	22 (35.5)	0.192
No training programme; n (%)	74 (46.8)	6 (40.0)	39 (48.1)	29 (46.8)	0,192

Unless expressed otherwise, results are shown as median and IQR

er specialists and for the general population (respectively). Self-evaluation of the work performed was outstanding and 91.9% drew pride from their work. However, 16.7% experienced regretted becoming intensivist (especially in hospitals with 200-500 beds) and up to 15% considered leaving their job.

Table 4 Personal perception of the impact of the ICUs response to the pandemic

	Total	Hospital beds			P
	N=246	<200	200-500	>500	
Has the opinion of hospital manager about the ICU improved? n (%)	152 (61.8)	13 (81.3)	72 (68.6)	67 (53.6)	0.040
Has the opinion of other colleagues about the ICU improved? n (%)	195 (79.3)	14 (87.5)	89 (84.8)	92 (73.6)	0.254
Has the opinion of general population about the ICU improved? n (%)	220 (89.4)	16 (100)	90 (85.7)	114 (91.2)	0.255
Evaluate your work during the pandemic (0-10)	8 (8, 9)	9 (8, 10)	8 (8, 9)	8 (8, 9)	0.171
Evaluate your ICU's work during the pandemic (0-10)	9 (8, 10)	8.5 (8, 9.75)	9 (8, 10)	9 (8, 10)	0.627
Evaluate the role of Intensive Care Medicine during the pandemic (0-10)	9 (9, 10)	10 (15.25, 10)	9 (9, 10)	9 (9, 10)	0.739
Have you regretted being an intensivist? n (%)	41 (16.7)	0 (0)	28 (26.7)	13 (10.4)	0.001
Have you considered leaving the speciality? n (%)	37 (15.0)	0 (0)	23 (21.9)	14 (11.2)	0.073
Have you felt proud to be an intensivist? n (%)	226 (91.9)	16 (100)	94 (89.5)	116 (92.8)	0.311
Relationship between ICU medical staff					
Worse; n (%)	74 (30.1)	0 (0)	28 (26.7)	46 (36.8)	
Better; n (%)	98 (39.8)	8 (50)	44 (41.9)	46 (36.8)	0,031
Same; n (%)	74 (30.1)	8 (50)	33 (31.4)	33 (26.4)	
Relationship between ICU medical and nursing staff					
Worse; n (%)	54 (22)	0 (0)	24 (22.9)	30 (24.0)	
Better; n (%)	98 (39.8)	10 (62.5)	38 (36.2)	50 (40.0)	0,160
Same; n (%)	94 (38.2)	6 (37.5)	43 (41.0)	45 (36.0)	

Unless expressed otherwise, results are shown as median and IQR

Impact of the pandemic on non-assistance activity and evaluation of activities and documents (Table 5). 64.2%, 85.8% and 76.8% of the participants consider that the pandemic has had a negative effect on fellow training, continuous medical education and on research, respectively.

DISCUSSION

The COVID-19 pandemic put a strain on healthcare systems in general and ICUs in particular, making it necessary to expand the capacity of both hospitals and ICUs. Our main finding is to quantify this expansion in the ICUs of Spain. A total of 67.7% of ICUs were expanded and the number of ICU beds was increased by 58.6% (a median of 9 beds per ICU). However, most beds were set up in open spaces: only hospitals with more than 500 beds increased the number of isolation single beds and virtually no new negative pressure beds were created. Wahlster et al., in their global survey obtained 2700 responses from a total of 77 different countries (86.1% of answers from North America, Europe and Central Asia), measured the overload more subjectively than us and found that 13% of those surveyed perceived ICU beds to be fewer than needed (from 11% of those from North America to 50% of those from East Asia and Sub-Saharan Africa). Additionally, 11%, 21% and 23% reported shortages of mechanical ventilation equipment, non-invasive mechanical ventilation and high flow oxygen therapy devices, respectively [22]. The material endowment of the Spanish ICUs was also increased, as recommended [23], but this increase in beds number and material resources is not correlated with increased availability of staff: medical staff only increased by 6.1%, and almost exclusively in hospitals with more than 500 beds. Similarly, the nursing ratio per patient increased only in 30.1% of units. The difficulty in hiring new staff was generalized. The approximation of Wahlster et al. is also more subjective and the lack of ICU medical and nursing staff is reflected in 15% and 32%, of their surveys, respectively [22].

Despite the minimal increase in staff, it was possible to treat 200% more patients over the ICUs baseline capacity (COVID-19 patients alone meant an increase of 175%). It is highly likely that this treatment overload is one of the most important factors that accounts for the high mortality reported in some Spanish series [4,5,24,25], as shown in the study by Bravata et al [8]. In a study conducted among ICU managers in Australia, it was estimated that the maximum possibility of increasing the number of ICU beds and ventilators was 191% and 120% in the country, respectively; and, to assume this expansion, an increase in medical and nursing staff of 245% and 269%, respectively, was considered necessary [26]. As we can observe, the estimated increase in beds is comparable to

Table 5 **Impact of the pandemic and opinion on activities and publications**

	Total	Hospital beds			P
	N=246	<200	200-500	>500	
Negative impact of the pandemic					
Fellow Training	158 (64.2)	1 (6.3)	65 (61.9)	92 (73.6)	<0.001
Continuous Medical Education	211 (85.8)	10 (62.5)	93 (88.6)	108 (86.4)	<0.001
Research in the unit	189 (76.8)	11 (68.8)	82 (78.1)	96 (76.8)	0.001
Do you agree with the following statements?					
On-line activities have been essential	201 (81.7)	16 (100)	79 (75.2)	106 (84.8)	0.178
On-line activities have modified the way COVID-19 is treated	150 (61.0)	14 (87.5)	63 (60.0)	73 (58.4)	0.029
On-line activities have led to more questions than answers	53 (21.5)	2 (12.5)	25 (23.8)	26 (20.8)	0.770
I prefer on-line to in person activities	76 (30.9)	8 (50.0)	30 (28.6)	38 (50.0)	0.440
There have been too many activities with little value	162 (65.9)	5 (31.3)	77 (73.3)	80 (64.0)	0.036
There have been too many low-level publications	206 (83.7)	10 (62.5)	91 (86.7)	105 (84.0)	0.081
There have been publications that led to difficulties treating patients	190 (77.2)	12 (75.0)	92 (87.6)	86 (68.8)	0.019
Have the following SEMICYUC documents been useful?					
Contingency plan for the intensive care services for the COVID-19 pandemic (11)	183 (74.4)	15 (93.8)	77 (73.3)	91 (72.8)	0.495
De-escalation plan for Intensive Care Units (40)	155 (63.0)	12 (75.0)	62 (59.0)	81 (64.8)	0.783
Recommendations of the Working Groups from the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) for the management of adult critically ill patients in the coronavirus disease (COVID-19) (13)	200 (81.3)	15 (93.8)	87 (82.9)	98 (78.4)	0.545
SEDAR-SEMICYUC consensus on the management of haemostasis disorders in severe COVID-19 patients (19)	158 (64.2)	15 (93.8)	61 (58.1)	82 (65.6)	0.144
Pharmacological treatment of COVID-19: Narrative review of the Working Group in Infectious Diseases and Sepsis (GTEIS) and the Working Groups in Transfusions and Blood Products (GTTH) (18)	170 (69.1)	13 (81.3)	68 (64.8)	89 (71.2)	0.747
Recommendations on cardiopulmonary resuscitation in patients with suspected or confirmed SARS-CoV-2 infection (COVID-19). Executive summary (17)	171 (69.5)	14 (87.5)	68 (64.8)	89 (71.2)	0.496
Ultrasound in the management of the critically ill patient with SARS-CoV-2 infection (COVID-19): narrative review (16)	143 (58.1)	11 (68.8)	51 (48.6)	81 (64.8)	0.130
Consensus document of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), the Spanish Society of Otorhinolaryngology and Head and Neck Surgery (SEORL-CCC) and the Spanish Society of Anesthesiology and Resuscitation (SEDAR) on tracheotomy in patients with COVID-19 infection (14)	122 (49.6)	13 (81.3)	46 (43.8)	63 (50.4)	0.189
Ethical recommendations for a difficult decision-making in intensive care units due to the exceptional situation of crisis by the COVID-19 pandemia: A rapid review & consensus of experts (15)	174 (70.7)	14 (87.5)	74 (70.5)	86 (68.8)	0.792
Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection (12)	174 (70.7)	15 (93.8)	72 (68.6)	87 (69.6)	0.414

Results are expressed as n (%)

the increase in patients we experienced in Spain. However, the increase in staff we attained is far from what is deemed necessary to treat such a large number of patients.

Fear for one's own health and the possibility of infecting one's family has accompanied ICU staff throughout this pandemic [22,27]. This is justified by the lack of IPE components, a common phenomenon all over the world during the initial waves of the pandemic [22,28]. Our data is along the same lines (in fact, only 25% of ICU did not have any staff infected). However, we also observed a significant decrease in this concern with the passing of time arising from better knowledge of the disease, more availability of supplies and vaccinations.

The combination of work overload, uncertainty over the management of patients and fear has resulted in an emotional

impact on ICU staff and this phenomenon appears to be generalized all over the world. Up to 52% of those surveyed by Wahlster et al. have felt emotional stress or exhaustion [22] and a survey performed among members of the *European Society of Intensive Care Medicine*, reports a prevalence of anxiety, depression and severe exhaustion symptoms of 46.5%, 30.2% and 51.0%, respectively [29]. From our survey we can deduce that the staff from average-sized hospitals were among those who were most impacted during the pandemic. They experienced the highest increase in beds and patients without having boosted their medical staff. This led to a 60% increase in the number of monthly guards per intensivist. It is precisely in medium-sized hospitals where more participants are detected who have regretted being intensivists. It is noteworthy that the percentage of intensivists who have considered leaving the specialty is lower than that reported in a survey conducted in Spain before the pandemic; in which 40.7% admitted having considered it [30].

In light of this situation, it is essential to have a structure that provides psychological support to ICU professionals as recommended in different documents [23,29,31]. More than half the hospitals offered a Psychological Support Unit and in most, multidisciplinary structures (COVID Committee) have been organised to take organisational decisions, whose work has in general been evaluated well.

From the patient management perspective, in 88% of hospitals the collaboration of specialities such as Anaesthetics, Cardiology, Paediatrics, Emergency Medicine and Pneumology, was necessary. Being aware of differences in training [32,33], the predominant treatment model (60.0%) was the one in which the ICU medical staff coordinated triage and led management of COVID-19 patients. In an attempt to improve treatment quality, training programmes were prepared for critical patient care in over half the hospitals. Despite the efforts made, there is a feeling that treatment quality has been negatively impacted both in Spanish and global ICUs. For example, changes occurred in the indication of mechanical ventilation in 16% of units and only 34% of ICUs maintained their usual policy of cardiopulmonary resuscitation [22].

Regarding non-care activity (research, education...), our results are contradictory. First, there is the general belief that the pandemic has made training and research more difficult (especially in medium-sized and large hospitals). Second, the switch from in person to online activities has been welcomed; activities carried out were evaluated positively and deemed useful as they helped update treatments received by COVID-19 patients. Furthermore, there is a predominantly critical position in regard to the "avalanche" of COVID-19 publications. 83.7% believe that material of low scientific and methodological quality was published; and 77.2% consider that some publications without the support of scientific evidence complicated the treatment of these patients, as pointed out in some editorials during the initial phase of the pandemic [34,35] and confirmed in a survey that highlighted heterogeneity in the management of these patients [36]. The efforts by SEMICYUC and its working groups in drawing up documents on management of the COVID-19 patient was welcomed.

The most important strength of our survey is the information provided about how the response to the pandemic was organized in Spanish ICUs, the differences between hospitals of different sizes and the approximate measure of the effort and extra cost that this entailed for the Intensive Care Units.

Among our work's limitations we should mention that taking part was voluntary and that the response percentage over the total membership was low (approximately 10%). Also, the answers reflect the individual perception of professionals taking part and may not represent all ICUs. However, we believe the sample does represent Spain as a whole as it includes hospitals of all sizes and every administrative region. In addition, the dynamic situation during the pandemic means that the situation reflected in the results must be considered limited to the time of the survey. No objective outcome indicators have been evaluated nor have they been linked to variables such as care overload or availability of new material; nor has the impact of the pandemic on the families of critically ill patients been assessed, what has showed to be extremely important [37].

In regard to the future, it is time to set out strategies that enable adapting medical and nursing staff and material resources to the new situation. The prevailing standards [38] and the number of places for Intensive Care Medicine fellow should be reviewed. It would also be convenient to provide our hospitals with the capacity to increase the staff (mainly through training programs or stable platforms that allow a faster incorporation of teaching material) and material resources depending on the needs [31,39].

It is essential and urgent to pay attention to the psychological condition of ICU workers, primarily, for health reasons, but also to avoid reducing the number of available staff, and for this it is necessary to have psychological support units, but also to improve communication and reduce care overload by adapting number of working staff to the so-called "new normality".

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CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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Comparación entre cinco técnicas de PCR para el diagnóstico del SARS-CoV-2

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RESUMEN

Introducción. Desde que aparecieron los primeros casos de SARS-CoV-2 son numerosas las técnicas que se han desarrollado para el diagnóstico o seguimiento de la infección, tanto técnicas directas como serológicas. La elección de una buena herramienta diagnóstica es fundamental para el control epidemiológico. El objetivo ha sido comparar cinco técnicas comercializadas de RT-PCR a tiempo real, en sensibilidad, especificidad y concordancia para la detección del SARS-CoV-2.

Material y métodos. Se compararon cinco kits comerciales de RT-PCR para la detección del SARS-CoV-2. Se tomaron ocho muestras positivas conocidas que se sometieron a siete diluciones o concentraciones diferentes y otras 135 muestras negativas para determinar valores de sensibilidad, especificidad y concordancia.

Resultados. La sensibilidad, especificidad, valor predictivo positivo (VPP) y valor predictivo negativo (VPN) para las técnicas de Palex, Roche y GeneXpert respecto a Seegene fueron idénticas, correspondientes a 98,21%, 100%, 100% y 99,26% respectivamente. Para Becton Dickinson la sensibilidad fue del 89,28%, la especificidad del 100%, el VPP del 100% y el VPN del 95,74%. La concordancia mediante el índice Kappa para Palex, Roche y GeneXpert fue del 0,9892, mientras que la concordancia para Becton Dickinson fue con un índice Kappa de 0,9215.

Conclusión. Todos los kits de RT-PCR comerciales presentaron elevadas sensibilidades y especificidades, así como VPP, VPN y concordancia.

Palabras claves: RT-PCR, SARS-Cov-2, comparación kits comerciales, pooling

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Comparison between five PCR techniques for the diagnosis of SARS-CoV-2

ABSTRACT

Introduction. Since the first cases of SARS-CoV-2 appeared, there have been numerous techniques that have been developed for the diagnosis or monitoring of infection, both direct and serological techniques. Choosing a good diagnostic tool is essential for epidemiological control. The objective was to compare five commercialized RT-PCR techniques in real time, in sensitivity, specificity and agreement for the detection of SARS-CoV-2.

Material and methods. Five commercial RT-PCR kits for the detection of SARS-CoV-2 were compared. Eight known positive samples were taken and subjected to seven different dilutions or concentrations, and another 135 negative samples were used to determine sensitivity, specificity, and agreement values.

Results. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the Palex, Roche and GeneXpert techniques with respect to Seegene were identical, corresponding to 98.21%, 100%, 100% and 99.26% respectively. For Becton Dickinson the sensitivity was 89.28%, the specificity of 100%, the PPV of 100% and the NPV of 95.74%. The agreement using the Kappa index for Palex, Roche and GeneXpert was 0.9892, while the agreement for Becton Dickinson was with a Kappa index of 0.9215.

Conclusion. All commercial RT-PCR kits had high sensitivities and specificities, as well as PPV, NPV, and concordance.

Key words: RT-PCR, SARS-CoV-2, commercial kits comparison, pooling

INTRODUCCIÓN

El coronavirus tipo 2 del síndrome respiratorio agudo grave (SARS-CoV-2) es un nuevo tipo de coronavirus aparecido a finales de 2019 y causante de la pandemia 2019-2020. Se trata de un virus respiratorio que produce en los pacientes desde casos asintomáticos portadores hasta neumonía bilateral grave con dificultad respiratoria que puede conducir a la muerte. Es un virus con una alta tasa de transmisibilidad y rápida propagación a través de secreciones respiratorias contaminadas y diseminadas por tos, estornudos, contacto entre personas infectadas o fómites contaminados [1].

Desde que apareció este virus de origen desconocido en la ciudad de Wuhan en China en diciembre de 2019, se han desarrollado numerosas técnicas para su diagnóstico o detección. Se han desarrollado tanto técnicas directas para detección de antígenos o genoma con PCR [2,3]. como técnicas indirectas para la detección de anticuerpos mediante inmunocromatografía o ELISA [4,5]. En este contexto de pandemia con rápida y gran propagación y gravedad en muchos de los pacientes, su diagnóstico rápido y certero se ha convertido en una pieza fundamental para el control epidemiológico de la enfermedad. Para ello, se ha considerado por su alta sensibilidad y especificidad como técnica de referencia la reacción en cadena de la polimerasa (PCR) sobre muestras respiratorias para la detección de casos activos. En concreto se trata de su variante RT-PCR, que requiere de una retrotranscripción ARN a ADN previa a la PCR, debido a su naturaleza de un virus ARN.

El objetivo del presente estudio ha sido comparar cinco técnicas comercializadas de RT-PCR a tiempo real, en sensibilidad, especificidad y concordancia para la detección del SARS-CoV-2.

MATERIAL Y MÉTODOS

Se compararon cinco técnicas comercializadas de RT-PCR a tiempo real para el diagnóstico del SARS-CoV-2 en términos de sensibilidad, especificidad y concordancia. Las cinco técnicas comparadas fueron Allplex™ 2019-nCoV Assay (Seegene), CerTest Viasure SARS-CoV-2 (Palex), Cobas® SARS-CoV-2 (Roche), BD MAX™ (Becton Dickinson) y Xpert® Xpress SARS-CoV-2 (Cepheid). Las técnicas de Seegene y Palex se realizaron en el termociclador a tiempo real CFX96 (Bio-Rad), la técnica de Roche se realizó en su plataforma Cobas 480, y las de Becton Dickinson y Cepheid en sus respectivas plataformas BD MAX y GeneXpert. Las técnicas de Seegene, Palex y Roche requirieron de extracción y purificación del genoma previo a la reacción, que se realizó mediante el extractor automático KingFhiser (Thermo Fisher Scientific) con el protocolo MagMAX CORE Nucleic Acid Purification Kit, a partir de 200 µl de muestra con 90 µl de eluído final. BD MAX y GeneXpert llevaban incorporados en sus kits y/o plataformas la extracción de ácidos nucleicos. Los tiempos totales de cada técnica fueron de 2 horas y 30 minutos para Seegene (incluida extracción 40 minutos), 2 horas y 20 minutos para Palex (incluida extracción), 1 hora y 50 minutos para Roche (incluida extracción), 2 horas y 30 minutos para Becton Dickinson y 50 minutos para GeneXpert.

La técnica de Seegene fue diseñada para detectar tres dianas de tres genes diferentes del virus, que fueron los genes E, RdRP y N. Palex fue capaz de detectar dos dianas correspondientes a los genes ORF1ab y N. Roche y Becton Dickinson utilizaron una sola diana para la detección del SARS-CoV-2 correspondientes a los genes N y S respectivamente, mientras GeneXpert utilizó dos dianas correspondientes a los genes E y N2. Todas las técnicas contenían su control interno de amplificación, aunque ninguno de ellos estaba diseñado para el control y calidad en la toma de muestra. La muestra estándar que se utilizó fue un hisopado nasofaríngeo [6] por paciente que se unieron en un mismo recipiente con medio de transporte para virus.

Para realizar el análisis de datos se tomó como método de referencia la RT-PCR de Seegene por presentar mayor número de dianas en su diseño y tener más posibilidades de detectar regiones diferentes del genoma del virus. Para establecer límites de detección relativos se tomaron 4 muestras verdaderas positivas conocidas procedentes de pacientes ingresados con clínica típica y diagnosticada por PCR y confirmadas por secuenciación. A las 4 muestras se le realizaron siete diluciones seriadas con suero fisiológico correspondientes a 1:1, 1:10, 1:100, 1:1000, 1:10000, 1:100000 y 1:1000000. Para determinar parámetros de especificidad relativa se tomaron 135 muestras negativas mediante PCR. Para calcular la concordancia se utilizó el índice Kappa.

RESULTADOS

Se analizaron un total de 191 muestras, 56 positivas (correspondientes a 8 muestras positivas en 7 diluciones o concentraciones distintas) y 135 muestras negativas. Los valores de sensibilidad, especificidad, valor predictivo positivo (VPP) y valor predictivo negativo (VPN) para las técnicas de Palex, Roche y GeneXpert respecto a Seegene fueron idénticas, correspondientes a 98,21%, 100%, 100% y 99,26% respectivamente. Para Becton Dickinson la sensibilidad fue del 89,28%, la especificidad del 100%, el VPP del 100% y el VPN del 95,74%. La concordancia mediante el índice Kappa para Palex, Roche y GeneXpert fue del 0,9892, mientras que la concordancia para Becton Dickinson fue con un índice Kappa de 0,9215. Todas las muestras negativas lo fueron por las cinco técnicas. Entre las 56 muestras positivas, 55 fueron detectadas también mediante Palex, Roche y GeneXpert, mientras que por Becton Dickinson se detectaron 50. En relación a los límites de dilución detectables, en todas las técnicas se detectaron en las cuatro muestras hasta la tercera dilución 1:1000. Mediante Palex y GeneXpert solo una muestra no fue detectada en la última dilución 1:1000000, mientras que por Roche también una muestra no fue detectada pero en la dilución 1:100000. Los datos detallados de positividad con su ciclo umbral de detección en cada una de las dianas en sus respectivas diluciones se presentan en la tabla 1. La diferencia media de CT en cada dilución 1:10 para cada una de las dianas y técnicas fueron de: 3,22, 3,11 y 2,89

Tabla 1 **Resultados de ciclo umbral (CT) de positivos de las distintas diluciones por las diferentes técnicas y genes diana.**

	Seegene			Palex		Roche	BD MAX	GeneXpert	
Gen diana (CT)	E	RdRP	N	ORF1ab	E	E	S	E	N2
M1 1	14,45	17,68	19,37	19,8	21,08	17,85	16,6	16,3	18,7
M1 1/10	18,5	20,57	22,52	23,82	25,36	20,94	20,9	19,1	21,2
M1 1/100	22,92	24,34	25,58	28,72	29,71	25,35	25,4	22,4	25,4
M1 1/1000	26,26	28,56	29,9	30,59	31,54	28,68	28,7	25,8	28,3
M1 1/10000	29,18	31,09	32,97	34,24	34,88	31,14	32,1	29,1	31,1
M1 1/100000	32,09	34,04	35,93	37,35	38,03	34,95	35,8	32,3	34,9
M1 1/1000000	35,24	37,13	39,24	39,85	40,35	38,36	39,1	35,6	38,2
M2 1	17,55	19,27	21,37	21,63	23,85	20,2	18,8	19,1	21,2
M2 1/10	20,97	22,73	24,98	25,01	27,06	23,6	23,4	21,9	24,3
M2 1 / 100	24,93	26,62	28,92	28,98	30,81	27,27	27,6	25,3	27,4
M2 1 / 1000	27,93	30,01	31,84	32,27	33,85	30,03	30,5	28	30,1
M2 1 / 10000	31,13	32,6	34,37	35,4	35,82	32,32	NEG	31,4	33,5
M2 1/100000	34,51	35,15	37,83	37,9	38,12	35,12	36,8	35,1	36,2
M2 1/1000000	37,88	38,33	39,84	40,84	40,96	38,84	NEG	37,8	39,6
M3 1	20,24	22,1	23,65	23,18	25,42	22,71	26,1	21	23,5
M3 1/10	24,17	26,05	27,32	27,23	29,28	26,23	27,7	23,8	26,4
M3 1/100	28,89	30,97	31,21	32,35	33,82	30,36	29,3	26,7	29,4
M3 1/1000	31,62	34	34,26	36,11	37,49	32,8	32,6	30,1	33,4
M3 1/10000	35,82	38,06	37,11	NEG	39,15	34,93	34,5	33,1	35,9
M3 1/100000	36,54	38,55	37,42	NEG	40,26	35,79	NEG	37	40,5
M3 1/1000000	NEG	37,71	NEG	NEG	NEG	36,49	NEG	NEG	NEG
M4 1	19,85	21,18	22,51	22,63	24,32	22,11	21,5	20,5	22,8
M4 1/10	22,13	24,54	25,19	25,56	26,91	24,78	24,3	24,6	27,8
M4 1/100	26,95	28,7	29,46	30,18	31,09	29,01	30,9	27,1	29,5
M4 1/1000	30,37	32,95	33,36	34,87	34,84	32,54	33,4	30	32,8
M4 1/10000	35,24	NEG	36,01	38,5	39,35	35,88	36,3	33,4	36,7
M4 1/100000	38,53	NEG	37,2	NEG	40,37	NEG	NEG	37,6	40,8
M4 1/1000000	NEG	36,24	37,72	NEG	40,12	35,35	NEG	NEG	43,3
M5 1	22,02	23,73	25,44	25,32	27,12	24,58	23,71	23,2	25,4
M5 1/10	24,38	25,87	28,13	27,44	30,17	26,84	27,81	26,1	28,1
M5 1/100	27,25	28,14	31,36	29,85	32,64	30,52	29,39	28,7	30,4
M5 1/1000	30,39	30,91	34,08	32,93	35,42	33,41	33,61	31,9	33,5
M5 1/10000	33,15	34,21	36,12	36,31	38,91	36,37	36,12	35,3	36,3
M5 1/100000	36,76	37,81	38,28	38,78	40,08	35,89	39,15	38,1	38,9
M5 1/1000000	38,96	39,41	NEG	40,81	40,56	38,27	NEG	40,2	41,8
M6 1	18,56	20,43	22,53	20,35	22,32	20,35	20,46	20,6	21,5

Tabla 1 **Resultados de ciclo umbral (CT) de positivos de las distintas diluciones por las diferentes técnicas y genes diana. (cont.)**

	Seegene			Palex		Roche	BD MAX	GeneXpert	
Gen diana (CT)	E	RdRP	N	ORF1ab	E	E	S	E	N2
M6 1/10	21,32	23,87	25,84	22,57	25,81	23,86	23,11	23,4	23,8
M6 1/100	24,59	28,49	27,95	25,96	28,9	25,45	26,84	25,6	27,4
M6 1/1000	27,98	32,45	31,85	29,84	33,49	29,72	29,43	28,8	30,5
M6 1/10000	30,58	35,86	35,81	33,67	35,42	33,71	33,51	32,8	33,9
M6 1/100000	34,3	35,45	NEG	35,89	38,88	36,8	35,86	35,5	38,7
M6 1/1000000	37,95	39,76	38,9	38,43	40,5	39,42	39,49	39,1	40,8
M7 1	20,7	22,42	23,68	22,68	24,12	22,85	22,8	22,1	23,8
M7 1/10	23,21	25,36	26,84	25,57	27,55	25,64	25,44	25,3	26,3
M7 1/100	25,86	28,94	29,47	28,13	30,22	28,98	27,33	28,4	29,2
M7 1/1000	28,43	32,11	33,56	31,18	33,47	32,71	30,52	30,1	31,9
M7 1/10000	32,58	35,14	35,64	34,52	35,94	35,85	33,42	33,4	35,2
M7 1/100000	36,74	37,45	36,41	37,09	38,63	37,46	36,75	37,5	38,6
M7 1/1000000	39,23	38,78	39,76	40,46	40,86	39,89	39,84	39,2	40,6
M8 1	21,3	23,53	24,63	23,68	25,36	23,04	23,11	22,9	23,6
M8 1/10	23,86	26,49	27,52	26,54	28,58	26,48	26,34	26,7	27,2
M8 1/100	26,49	29,82	30,48	29,87	31,22	29,71	29,86	29,5	30,5
M8 1/1000	29,74	31,76	33,79	32,41	34,12	32,88	32,62	32,9	33,9
M8 1/10000	32,53	34,83	37,96	35,84	36,82	35,42	35,57	35,6	37,6
M8 1/100000	35,86	37,4	39,84	36,94	38,66	37,34	38,98	38,4	39,4
M8 1/1000000	37,87	39,06	NEG	39,83	40,43	39,48	NEG	40,1	NEG

M1= muestra 1, M2= muestra 2, M3= muestra 3, M4= muestra 4, M5= muestra 5, M6= muestra 6, M7= muestra 7, M8= muestra 8.

para los genes E, RdRP y N respectivamente para Seegene; 3,21 y 2,78 para los genes ORF1ab y E respectivamente para Palex; 2,98 para el gen E de Roche; 3,2 para el gen S de BD MAX; 3,07 y 3,12 para los genes E y N2 respectivamente para GeneXpert.

DISCUSIÓN

En el presente estudio se compararon cinco kits comerciales para la detección del genoma del SarsCov-2 mediante RT-PCR en muestras clínicas. La serie de las 28 muestras positivas estaba compuesta a su vez por cuatro muestras con elevadas cargas virales relativas iniciales deducidas por sus bajos CTs en la reacción en torno al ciclo 20. Las cuatro muestras se diluyeron de forma seriada hasta 1:1000000 con la finalidad de comparar los límites de detección relativos entre las cinco técnicas estudiadas.

La técnica de Seegene fue capaz de detectar todas las diluciones de las cuatro muestras en al menos una de sus tres dianas, demostrando ser la más sensible de las cinco comparadas, y que por ello se consideró de referencia para el cálculo de las sensibilidades y especificidades de los demás kits comerciales estudiados. Los kits de Roche, Palex y GeneXpert mostraron idénticos valores de sensibilidad, especificidad, VPP y VPN, destacando la alta sensibilidad de los tres incluso en las diluciones más altas. Sin embargo, el kit de BD aunque mostró excelentes valores de especificidad, VPP y VPN, obtuvo un valor de sensibilidad algo más bajo en torno al 80%, no detectando el virus en las diluciones más altas de algunas de las muestras. Aunque hay que destacar que la plataforma BD MAX aporta la ventaja de realizar extracción genómica y amplificación en un solo paso de manipulación [7] pudiéndose realizar análisis individuales de urgencias al igual que GeneXpert [8].

Una de las principales limitaciones de los cinco kits comerciales comparados fue que ninguno contiene un sistema de control interno que verifique la calidad de la muestra, que demuestre que la muestra contiene células humanas mediante la incorporación de sondas y cebadores dirigidos a la detección de algún gen constitutivo humano. Como sería el caso del gen RNasa P comúnmente utilizado en PCR para la detección de virus respiratorios [9,10]. En este sentido, la sensibilidad de dichas pruebas puede verse afectadas por la falta de control de calidad de la muestra.

La concordancia en general fue excelente entre los cinco kits con un índice Kappa cercano al uno, aunque BD presentó un índice algo inferior debido a su menor sensibilidad mostrada. Otros estudios comparativos entre diferentes PCR para la detección de SARS-CoV-2 mostraron similares índices Kappa de concordancia a los del presente estudio, oscilando los índices entre 0,9 y 1 [11,12].

Por otra parte, en las diluciones seriadas al 1:10, la media de incremento de los CT en cada dilución para las diferentes dianas de todos los kits comerciales comparados osciló entre 3 y 3,5 por dilución, siendo concordante con un estudio chino [13] en el que también realizaron diluciones seriadas al 1:10 con incrementos de CT para las diferentes técnicas comparadas de 3,33 y 3,13. En el presente estudio se observa en la tabla 1 que en muchas de las dianas, el incremento de CT en las últimas diluciones es menor a la media, observándose en algunos casos hasta incrementos negativos. Estos datos hacen reflexionar sobre la posibilidad de utilizar técnicas de *pooling* para optimizar los recursos sin perder sensibilidad significativa como han demostrado algunos estudios [14,15], aunque en el presente estudio se trata de una consideración teórica y que su utilidad dependerá de la prevalencia esperada.

En conclusión, todos los kits de RT-PCR comerciales comparados presentan elevadas sensibilidades y especificidades, así como VPP, VPN y concordancia. Aunque con el kit de Seegene se obtuvo la mayor sensibilidad, siendo capaz de detectar todas las diluciones de las muestras positivas. Todos los kits, incluso diluyendo las muestras 1000 veces, fueron capaces de detectar el genoma del virus, por tanto, podría considerarse la posibilidad de realizar *pooles* de 5-10 muestras para optimizar el rendimiento en el cribado del virus.

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CONFLICTO DE INTERESES

Los autores declara no tener conflicto de intereses.

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Letter to the Editor

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The importance of an early gastroenteritis diagnosis to discard MIS-C during SARS-CoV-2 pandemic

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Sir,

It is important to highlight the clinical significance of rapid microbiological tests such as those based on polymerase chain reaction which provide an early diagnosis, avoid unnecessary tests and therapies and discard worse-prognosis diseases such as multisystem inflammatory syndrome in children (MIS-C) [1].

In this respect, we describe four cases of children aged between five- and eight-years old presenting with fever and gastrointestinal symptoms (abdominal pain, vomiting and non-bloody diarrhea) during SARS-CoV-2 pandemic in the Hospital Universitario Central de Asturias, northern Spain (Table 1). They all presented tachycardia but had good general condition although affected by pain. Abdominal examination was anodyne except in one of them. Laboratory tests showed an elevated C-reactive protein (all patients), lymphopenia (three patients), high procalcitonin values (two), high fibrinogen levels (two) and hypertransaminasemia (one). In a single case the analytical study was extended and an elevation of D-dimer and B-type natriuretic peptide was observed. The latter one had been contacted with SARS-Co V-2 patient in the previous two weeks while another one had past confirmed CoV-2 infection two months before and had IgG antibodies. All cases were initially considered as suspected MIS-C. Nevertheless, a stool sample was early sent to the clinical microbiology laboratory, the FilmArray Gastroinstestinal Panel (BioFire Diagnostics) was performed and a *Campylobacter jejuni* was informed in all of them within the first two hours after admission.

The Centers for Disease Control and Prevention (CDC) published a case definition for MIS-C which included fever, multi-organ involvement and laboratory data of inflammation [2]. This definition was meant to be sensitive but no so specific [3]. Fever and gastrointestinal are the most common symptoms in MIS-C but also from many other diseases. Although the CDC definition includes multi-organ involvement, this may not be present at the beginning and might develop later. A recent exposure to SARS-CoV-2 could help to guide the diagnosis, but this is not always proven and IgG is usually positive but not universally [3].

In our center, when MIS-C is suspected, a basic analysis is initially performed and depending on its results and the patient evolution, further investigations included some blood inflammatory markers tests and SARS-CoV-2 serology. In the aforementioned cases, tests were carried out in a staggered way since patients were stable, they were admitted under observation, monitored and in addition, the stool results were obtained early. In addition to provide a prompt diagnosis, rapid stool results can avoid unnecessary diagnostic tests and IVIG administration, which is not harmless and entails risks such as anaphylaxis, thrombosis, and hemolysis [4].

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None to declare.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Table 1 **Patient characteristics and laboratory findings**

Characteristics	Case 1	Case 2	Case 3	Case 4
Demographic				
Sex	Male	Male	Male	Female
Patient age (years)	8	4	6	5
SARS-CoV-2				
Exposure	Yes (2 weeks)	No	No	Unknown
Infection	No	No	No	Yes (2 months)
Presenting symptoms				
Days of fever at presentation	3	1	4	2
Abdominal pain	Yes	Yes	Yes	Yes
Vomiting	Yes	Yes	No	Yes
Diarrhea	No	No	Yes	Yes
Admission laboratory values				
WBC (x 10^3/mcL)	11.37	8.64	10.78	6.86
Hgb (g/dL)	14.3	11.7	12.9	12.2
Platelets (x 10^3/mcL)	253	213	254	359
Neutrophils (cells/mm^3)	9,000	6,890	8,450	3,970
Lymphocytes (cells/mm^3)	930	1,070	950	2,260
CRP (mg/dl)	2.9	6.7	3.2	6.8
Procalcitonin (ng/ml)	0.3	0.77	0.42	10.3
SARS-CoV-2 RT-PCR	Negative	Not done	Negative	Negative
SARS-CV-2 antibody	Negative	Not done	Negative	Positive
Stool studies (Filmarray GI)	*Campylobacter*	*Campylobacter*	*Campylobacter*	*Campylobacter*, Enteropathogenic *E. coli*
Stool studies (Culture)	*C. jejuni*	*C. jejuni*	*C. jejuni*	*C. jejuni*

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Letter to the Editor

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Erratic enteric absorption of dolutegravir in a critically ill patient

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Sir,

The life expectancy of HIV-infected patients has increased over recent years [1], as a result, patients' now access health care facilities which were previously limited to them, such as the intensive care unit (ICU) where admission rates have increased during the last decade. ART's lifesaving role in ICU is a controversial topic [2]. A recent meta-analysis reported better outcomes both on short-term and long-term mortality in patients treated with ART during their ICU stay [3].

We present a case of an HIV-patient admitted to the ICU with undetectable plasma concentrations of dolutegravir (Cp-DTG) along the entire dose range. A 32-year-old obese (body mass index=30kg/m^2) Turkish male was diagnosed with lymphoma with plasmablastic differentiation, tumor lysis syndrome, and septic shock. Since the HIV diagnosis one month before, the patient was on dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) one of the preferred first-line regimen for adults in international guidelines. DTG/ABC/3TC was introduced into the ICU medication and was administered by nasogastric tube (NT).

As is routine in our clinical practice, we analyzed the Cp-DTG, as well as of the other drugs (meropenem, linezolid and anidulafungin), in our institution with high-performance liquid chromatography validated method in order to guarantee correct concentrations. The plasmatic drug concentrations were measured on the fourth day of admission to the ICU when all drugs had reached steady state.

The fact we observed detectable plasma concentrations for the intravenous drugs analyzed (meropenem concentration through (through) and Cpeak were 12.4 mg/L and 35,4 mg/L, linezolid C through and Cpeak were 1.7 mg/L and 11.9 mg/L, and anidulafungin Cthrough and Cpeak were 2.1 mg/L and 5.8 mg/L), and that the CpDTG were undetectable including the peak representing enteric absorption could be related to several factors, including pathophysiological and pharmacological.

Pathophysiological factors are discussed:

Inflammation and immunosuppression status: This situation could occur derived from inflammation and immunosuppression in critically ill patients, which may alter drug metabolizing enzymes, transporters, fluid shifts, and plasma proteins (PP)[4].

Our patient presents acute inflammation derived from septic shock and tumor lysis syndrome, as demonstrated with the biomarker's elevation such as ferritin (123280ng/mL), C-Reactive protein (24mg/dL), D-dimer (5359mcg/mL) and procalcitonin (91ng/mL).

Enteric malabsorption: It could be a consequence of mesenteric hypoperfusion originated by redistribution of blood flow away from the gastrointestinal tract in order to regulate cardiovascular homeostasis in the presence of shock [5]. This can be reflected in hyperlactatemia determination as well as high norepinephrine requirements, both up to values of 9.5mmol/L and 3.6mg/hour respectively. In this context, our patient received trophic enteral feeding (EF) because high gastric retention episodes. EF intolerance was presented for days and could lead to atrophy of the intestinal mucosa, causing decreased dolutegravir absorption.

Drug distribution and elimination alterations: Critical illness-related increased leakage of plasma (albumin=1.4g/dL) and invasive mechanical ventilation as is the case presented, is not expected to influence the dolutegravir distribution volume (Vd) due to its lipophilia (logP=2.2). Our patient could present intensely increased dolutegravir clearance as a result of severe hypoalbuminemia and hyperbilirubinemia (4.5mg/dL) due to significant dolutegravir binding to PP (≥98.9%).

Fever: As the effect of hypothermia-mediated alterations in the cytochrome P450 enzymes [6] has been described, high

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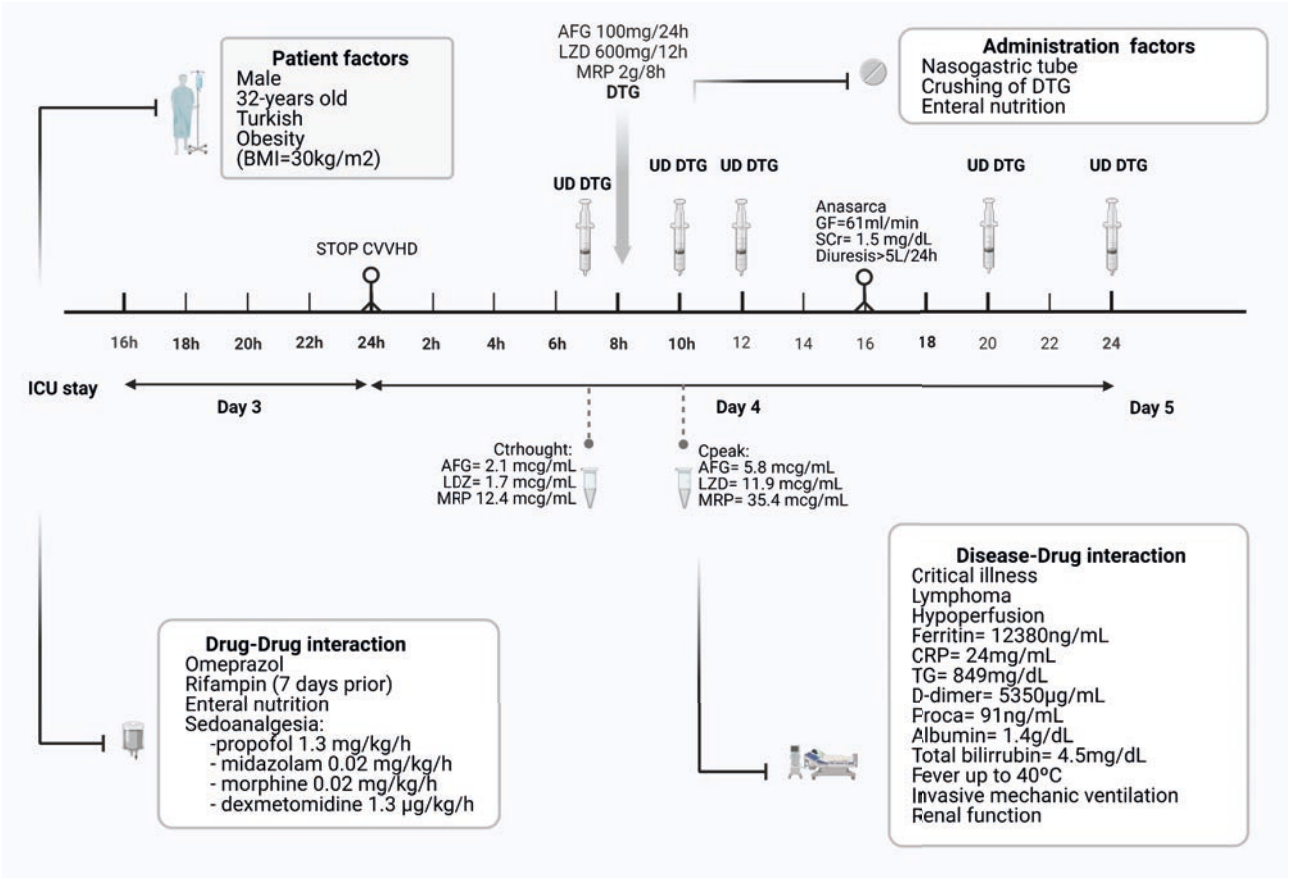

Figure 1 | **Factors influencing the pharmacokinetics of dolutegravir**

AFG=anidulafungin; BMI=body mass index; CRP= C-Reactive protein; CVVHD= continuous venovenous hemodialysis; DTG=dolutegravir; GF=glomerular filtration; HIV= human immunodeficiency virus; LDZ=linezolid; MRP=meropenem, Proca=procalcitonin; UD=undetectable; SCr=serum creatinine; TG=triglycerides

and persistent fever (up to 40ºC) in our patient could be a disturbing factor.

Haematological malignancies: These may interact with some drugs increasing their Vd and clearance [7], however, lymphoma impact on dolutegravir pharmacokinetics is unknown.

Pharmacological aspects are discussed:

NT drug administration: This strategy is usually required in critical patients. Currently, only zidovudine is formulated intravenously, and, in most cases, antiretroviral tablets are manipulated for administration in the absence of data on their impact. Based on the experience of Roskam-Kwint *et al.*, dolutegravir administration by NT wouldn't be a contributing factor to the undetectable CpDTG observed because crushing DTG/ABC/3TC leads to a higher dolutegravir concentrations unaffected by enteral nutrition [8]. This trial was performed with healthy volunteers ignoring disturbing factors involved in real practice, such as disease-drug and/or drug-drug interactions.

Sedoanalgesia drugs: It can cause a delay in gastric emptying, slowing dolutegravir absorption. Prokinetic drugs weren't introduced until several days after dolutegravir determination, so they couldn't have caused any impact on absorption.

Drug-drug interactions: Dolutegravir absorption is not acid-dependent, therefore, alkalinization of the gastric pH derived from omeprazole stress ulcer prophylaxis [5] of the critically ill patient isn't expected to alter its bioavailability.

The patient was treated with rifampin seven days before CpDTG determination and double dose dolutegravir were reduced immediately after its suspension. Despite rifampicin induction dissipates two weeks after discontinuation [9], this doesn't explain the lack of dolutegravir absorption detected.

Other factors*:* Data on specific dolutegravir dosage adjustments based on ethnicity, obesity and hepatic/renal function are lacking. It should be noted that the patient was subjected to continuous venovenous hemodialysis hours prior to CpDTG determination, however minimal dolutegravir removal by hemodialysis is expected [10]. Moltó *et al,.* [10] measured both

predialyzer, postdialyzer CpDTG and DTG concentrations in the dialysate from 5 HIV-infected patients with end-stage renal disease. Moló *et al,.* [10] observed a median DTG hemodialysis extraction ratio of 7%, negligible DTG concentrations in the dialysate, and a CpDTG postdialyzer 34,1 times above the protein-binding-adjusted inhibitory concentration. Their data suggests that no specific dolutegravir dosage adjustments are required in hemodialysis.

The minimal removal of DTG by hemodialysis technique is consistent with its physicochemical characteristics [10] due to it is highly binding to PP and a molecular weight of 419.38 g/mol. In addition, it is minimally eliminated by the kidneys (<1% unchanged).

To our knowledge, this is the first case reported demonstrating the impact of critical illness-related enteric malabsorption on DTG by measuring drug levels. The patient was extraordinarily complex, like many ICU patients. It is essential to study ART pharmacokinetic behavior in critical illness, especially in the absence of intravenous formulations.

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Síndrome de absceso hepático asociado a colecistitis por *Klebsiella pneumoniae* hipervirulenta K1 ST23

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Mujer de 62 años, natural de Colombia y antecedentes médicos de hipertensión arterial, diabetes mellitus tipo 2 y lupus discoide sin tratamiento médico, que acudió a urgencias por cuadro de 3 días de evolución. Refería fiebre de 39ºC, dolor abdominal y costal derecho con inicio 72 h antes. Presentaba tensión arterial de 118/60 mm Hg, frecuencia cardiaca de 101 lpm, 17 rpm, temperatura de 39ºC y saturación de O_2 de 98 %. En la exploración física, destacaba dolor a la palpación profunda en hipocondrio derecho. En analítica de sangre se observaba una proteína C reactiva de 106 mg/L (0-5), procalcitonina de 24,8 ng/mL (0-0,5), GPT de 48 U/L (5-31), fosfatasa alcalina de 87 U/L (35-104), GGT de 73 U/L (7-42), INR de 1,4 (0,9-1,2) bilirrubina de 1,9 mg/dL (<1,2) con neutrofilia del 67% (43-65) y 7,77x10^3 leucocitos (4,5-11). Se recogieron muestras para cultivo y se decidió realizar una tomografía computarizada (TC) con contraste intravenoso abdomino-pélvica, en la que se describían múltiples colelitiasis. Además, se observó colección hepática compatible con absceso infeccioso de hasta 6,7 cm (figura 1), junto con otra pequeña colección de hasta 2 cm en segmento 8 y signos inflamatorios compatibles con peritonitis. Una hora después de su llegada a urgencias la paciente recibió una dosis intravenosa mediante piperacilina/tazobactam (4 g/0,5 g) y fue ingresada ante diagnóstico de colecistitis aguda complicada con absceso hepático (clasificación de gravedad de colecistitis aguda grado II según las guías de Tokyo). Se decidió colecistectomía por vía laparoscópica (cálculo enclavado en infundíbulo) y punción de colección tabicada de 6,7 cm. Durante la intervención, se halló cirrosis macronodular en hígado no conocida previamente. En el informe de anatomía patológica se describió pieza de colecistectomía de 12,5 x 4 x 3 cm, en cuyo interior se identificó contenido biliar y múltiples litiasis que medían entre 1 y 2,5 cm, con pared de 0,2 cm y mucosa de coloración pardo clara. Microscópicamente, el epitelio columnar estaba conservado con infiltrado inflamatorio agudo y crónico subepitelial.

Tanto en muestra de hemocultivo como en la procedente del absceso hepático se aisló *Klebsiella pneumoniae*. La susceptibilidad antimicrobiana fue estudiada mediante la técnica disco difusión en agar Mueller-Hinton (Becton Dickinson, Franklin Lakes, NJ, USA) y mediante el panel automatizado ID/NMIC 503 del sistema BD™ Phoenix (Becton Dickinson, Franklin Lakes, NJ, USA). El aislado sólo presentaba resistencia a ampicilina.

Se realizó "*String test*" para predecir el fenotipo hipermucoviscoso dada la apariencia macroscópica de la cepa en los cultivos y el tipo de cuadro invasivo, resultando positivo. La cepa procedente del hemocultivo fue enviada para estudios complementarios al "Centro Nacional de Microbiología" (Instituto de Salud Carlos III). Realizaron secuenciación genómica completa, que confirmó la ausencia de mecanismos de resistencia y que pertenecía al serotipo capsular K1 y MLST 23 (tipificación multilocus de secuencias, útil en epidemiología molecular para filiación de brotes). Además, la cepa poseía genes de virulencia característicos del patotipo hipervirulento de *K. pneumoniae* como *rmpA* y *rmpA2* (regulador del fenotipo mucoide A, responsable de la hipermucoviscosidad de la cepa), IucABCD-iutA (que forman el complejo operón de la aerobactina, sideróforo) e iroBCN (perteneciente al cluster de genes de salmochelina, sideróforo), localizados en plásmidos.

Durante su hospitalización continuó con piperacilina/tazobactam (4 g/0,5 g cada 6 h IV), y evolucionó de manera favorable desde el punto de vista analítico y clínico (afebril y disminución de proteína C reactiva de 106 mg/L a 80 mg/L), pero a los 6 días decidió alta voluntaria sin tratamiento alguno tras episodio delirante.

Acudió de nuevo a urgencias 3 días después por aumento de perímetro abdominal y salida abundante de líquido ascítico a través de herida quirúrgica. En TC abdominal se observó co-

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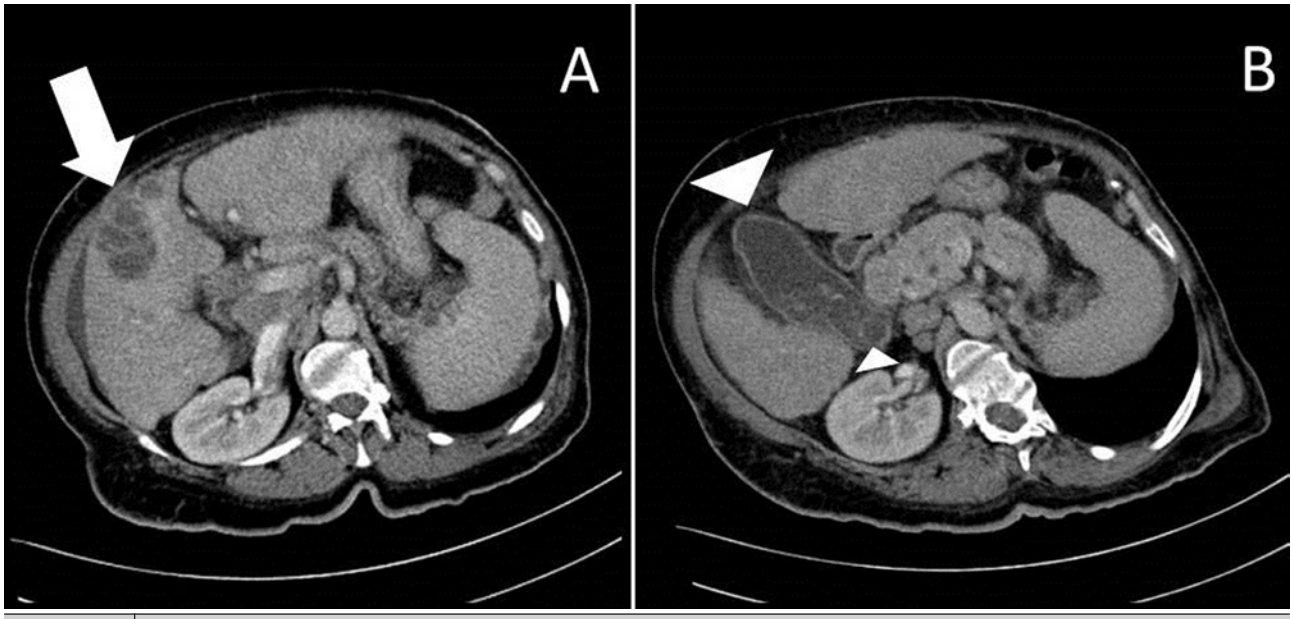

Figura 1 | **Imágenes axiales de TC- abdominopélvico con contraste intravenoso.**

Figura 1A: se aprecia una colección multiquística con realce periférico dentro del segmento IV hepático (flecha). Muestra el aspecto característico en «racimo de uvas» de un absceso hepático.
Figura 1B: Agrandamiento difuso y engrosamiento de la pared hipodensa de la vesícula biliar (punta de flecha grande) con acúmulo de grasa periférica y realce de la mucosa, compatible con colecistitis. En su interior se aprecian múltiples nódulos hipodensos subcentimétricos compatibles con cálculos biliares (pequeña punta de flecha).

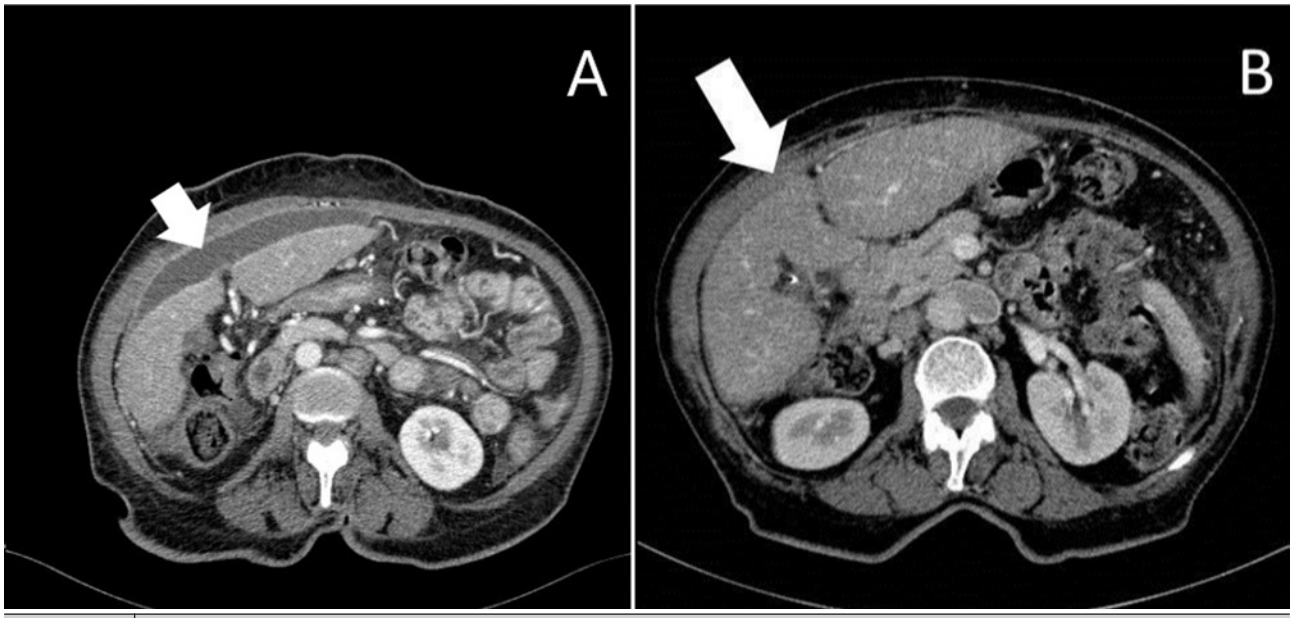

Figura 2 | **Imágenes axiales de TC- abdominopélvico con contraste intravenoso.**

Figura 2A: se observa colección flemonosa que ha aumentado respecto a estudio previo con zona nodular con mayor captación de contraste de unos 6 x 4 x 12 cm (flecha blanca).
Figura 2B: resolución completa del absceso hepático, con aspecto normal del segmento IV (flecha en imagen B).

lección lobulada residual de 2 x 2 cm, moderada cantidad de líquido ascítico y signos de peritonitis. En analítica de sangre destacaba proteína C reactiva de 231 mg/L y 20,3x10^3 leucocitos, siendo ingresada por descompensación ascítica con piperacilina/tazobactam como tratamiento intravenoso (4/0.5 g cada 6 h). Se realizó ecografía para realizar paracentesis diagnóstica pero no se observó ascitis a través de esta técnica. La paciente continuó con dolor moderado, febrícula (37,5ºC) e hipotensión (88/40 mm Hg) tras 7 días de hospitalización y con salida de líquido seroso a través de herida quirúrgica. Se realizó cierre por segunda intención de herida quirúrgica. En TC de control (figura 2A), se observó colección flemonosa que había aumentado respecto estudio previo de unos 6 x 4 x 12 cm, que se acompañaba de colecciones perihepáticas (una en cúpula de 5 x 0,8 cm y otra subcapsular de 1,9 x 17 cm en los segmentos IV B y V). Se intentó realiza drenaje de la colección subcapsular tabicada con salida de líquido ascítico que se envió al laboratorio de microbiología (10-25 leucocitos por campo) con cultivos negativos y administración de uroquinasa (16 días después de la cirugía y el drenaje de la primera colección). En este momento se decidió escalada antibiótica a meropenem (1 g cada 8 h IV).

Después de 7 días los valores analíticos disminuyeron (proteína C reactiva 5,6 mg/L y leucocitos de 5,6x10^3) realizándose otro TC que mostró reducción del tamaño de la colección perihepática (figura 2B) con desescalada antibiótica a piperacilina-tazobactam (4 g/0,5 g cada 6 h IV) y mejoría clínica. La paciente decidió alta voluntaria tres semanas después del inicio del cuadro con ciprofloxacino (500 mg cada 12 h durante 2 semanas por vía oral) como terapia secuencial antibiótica con clasificación Child-Pugh B, siendo derivada a las consultas de hepatología para control estricto.

Las infecciones por el patotipo de *K. pneumoniae* hipervirulento (hvKp) presentan mayor virulencia y causan con mayor frecuencia enfermedad invasiva que las cepas clásicas. Se describió por primera vez en la década de los 80 en Asia, donde se considera enfermedad endémica actualmente [1].

El factor de virulencia que define a este tipo de cepas es la elevada producción de polisacárido capsular, que les confiere la propiedad de hipermucoviscosidad y resistencia a la opsonofagocitosis del suero humano [2]. Esta característica puede estar codificada en cromosomas como el gen *magA* (gen A asociado a la mucoviscosidad, perteneciente a un clúster específico del serotipo capsular K1) o en plásmidos como el gen *rmpA/rmpA2* (regulador del fenotipo mucoide). Otros factores de virulencia son la producción de sideróforos (que aumentan la supervivencia bacteriana como aerobactina o salmochelina, siendo característicos de estas cepas). El "*String test*" permite predecir en la mayoría de los casos la asociación de los aislados con la hipervirulencia, aunque en un pequeño porcentaje esto podría no ocurrir así. De modo que Li G et al sugieren que sería más eficiente utilizar tanto el *"String test"* como la detección del gen de virulencia *rmpA* y/o sideróforos para poder detectar todas las cepas hvKp [3].

La cepa del caso pertenecía al grupo clonal ST23, conocido por presentar algunas cepas multirresistentes y causa de infección nosocomial, pero en nuestro caso la cepa estudiada era sensible a todos los antibióticos testados [4,5]. De todos los serotipos capsulares descritos en *K. pneumoniae,* la mayoría de casos son producidos por los serotipos capsulares K1 y K2. El síndrome de absceso hepático asociado a infección diseminada o metastásica como endoftalmitis, meningitis o absceso cerebral se antoja como una de las entidades clínicas más características, endémica en Asia [1,6]. Otros cuadros diferentes como neumonías complicadas con cavitaciones/necrotizantes o con empiema, abscesos (hepáticos, prostáticos, cerebrales o esplénicos, entre otros), colecistitis/colangitis también se han visto asociados a hvKp [7,8]. En nuestra institución recientemente hemos podido filiar este patotipo en un caso de neumonía cavitada asociado a bacteriemia y en otro de neumonía necrotizante

La diabetes mellitus, los catéteres y la enfermedad hepatobiliar previa son un factor de riesgo para el desarrollo de estas infecciones, aunque puede ocurrir también en pacientes previamente sanos [9]. Precisamente nuestra paciente presentaba tanto diabetes mellitus tipo 2 como cirrosis macronodular. El tratamiento de estas infecciones consiste en antibioterapia dirigida durante 4-6 semanas junto con el control del foco mediante el drenaje de las colecciones [10]. En el caso que presentamos la paciente presentó una recidiva de los abscesos hepáticos a pesar del primer drenaje realizado. La existencia de otros focos de infección en forma de abscesos más pequeños que no fueron drenados, la insuficiente duración del tratamiento antibiótico y las características del fenotipo hipervirulento de *K. pneumoniae* (factores de virulencia que permiten una mayor supervivencia de la cepa y más facilidad para producir cuadros invasivos) pueden ser la causa de esta recidiva.

En situaciones complejas como cepas extremadamente resistentes o dificultad de los antibióticos para alcanzar el sitio de infección se podrían utilizar terapias diferentes y/o adyuvantes al tratamiento tradicional como es el caso de la inmunización pasiva o activa mediante anticuerpos monoclonales o vacunas o el uso de terapias con bacteriófagos [11,12].

Como conclusión, las infecciones por el patotipo hvKp suponen cada vez un problema mayor a nivel mundial. La detección y el tratamiento precoz son puntos clave para evitar la diseminación de estas cepas y con ello, evitar la diseminación de resistencias antibióticas, plásmidos de virulencia y consecuencia fatales en todo tipo de pacientes. El avance de nuevas herramientas diagnósticas y terapéuticas es clave y requiere de una colaboración entre los clínicos y los laboratorios.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de interés.

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Letter to the Editor

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Herpes zoster complicated with aseptic meningitis after cardiac transplantation: Report of two cases and review of the literature

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Sir,

Varicella-Zoster Virus (VZV) is a frequent cause of morbidity in solid organ transplant (SOT) recipients, especially after heart transplant (HTx) [1]. Both VZV primoinfection and reactivation can entail visceral involvement [2]. We describe two cases of HTx recipients who developed Herpes Zoster (HZ) with associated meningitis, a condition of unknown prevalence and prognosis in this population.

Patient #1, a 45-year-old man, underwent HTx in September 2018 due to familial transthyretin amyloidosis with advanced heart failure. Maintenance immunosuppressive therapy (IST) was based on tacrolimus, mycophenolate mofetil (MMF) and prednisone. After HTx he suffered progressive cytopenias, making it necessary to down-titrate MMF. The patient had an intermediate risk citomegalovirus (CMV) serostatus (donor +/recipient +), so a preemptive therapy approach was followed in order to avoid further hematologic toxicity.

Five months after HTx the patient was admitted with a 2-day history of fever and vesicular rash suggestive of disseminated HZ affecting right cervical and dorsal regions (Figure 1A-B). He also had cephalea, nausea, photophobia and neck stiffness, but no neurological deficit at examination. Blood tests were unremarkable. Intravenous acyclovir (10 mg/kg/8h) was started and lumbar puncture was performed because of suspected central nervous system (CNS) involvement. Analysis of cerebrospinal fluid (CSF) showed 13 leukocytes/mL with 88% of mononuclear cells, glucose of 49 mg/dL and proteins 108 mg/dL. Qualitative polymerase chain reaction (q-PCR) on a CSF sample was positive for VZV-DNA. Bacterial and fungal cultures were sterile. Cerebral magnetic resonance was normal, so disseminated HZ with associated meningitis was diagnosed and IST down-titrated. He completed a 3-weeks course of antiviral therapy, with complete resolution of cutaneous lesions and meningeal symptoms. No further VZV-reactivations have been observed during follow-up.

Patient #2, a 72-year-old female, underwent HTx in August 2018 due to familial dilated cardiomyopathy with advanced heart failure secondary to a pathogenic variant in RBM20, a gene that encodes RNA-binding motif protein 20, which regulates the splicing of several sarcomeric genes. After HTx she developed multifactorial severe renal dysfunction. At discharge she was receiving MMF, prednisone and tacrolimus. The patient had an intermediate CMV risk profile (donor -/recipient +), so a preemptive therapy strategy was adopted in order to avoid further renal toxicity

Thirteen months after HTx she presented with HZ affecting left D6-D8 dermatomes. She also suffered mild cephalea, in this case without meningeal symptoms. Neurological examination was unremarkable. Laboratory tests showed normal leukocyte count, liver function parameters and C-reactive protein. Lumbar puncture was performed because of persistent cephalea. CSF analysis showed no pleocytosis and normal levels of glucose and proteins, but q-PCR was positive for VZV-DNA. Bacterial and fungal cultures were sterile. Cerebral computed tomography showed a normal cerebral parenchyma without focal lesions. Thus, VVZ subclinical meningitis associated to HZ was diagnosed. She received a 14-day course of intravenous acyclovir adjusted to renal function, with complete resolution of the cutaneous lesions and cephalea. Nowadays she remains asymptomatic and free from further VZV-reactivations.

We describe two cases of HTx recipients with HZ and only mild neurological symptoms who were diagnosed with VZV-meningitis and who had good clinical course under antiviral therapy. VZV is nowadays recognized as one of the most common causes of aseptic meningitis in general population, where it has a better prognosis than meningoencephalitis [3-6]. Nev-

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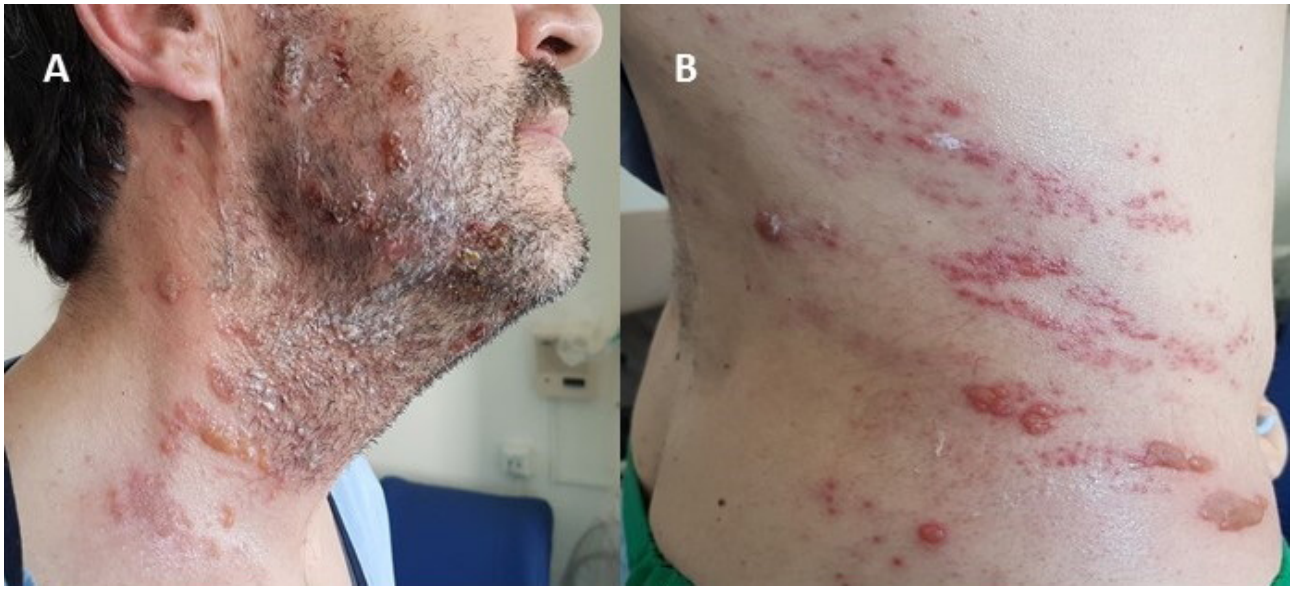

Figure 1 | **Physical examination findings of Patient #1. Disseminated HZ affecting C2-C3 (A) and D10-D12 (B) dermatomes.**

ertheless, it is risky to assume such good outcomes in SOT recipients with meningitis, since immunocompromised patients are underrepresented in general population series and studies focused in SOT recipients are lacking. A case series of VZV-CNS infection after SOT, by Kang et al, described 12 meningoencephalitis cases with poor prognosis: 33% of patients died due to the infection, 17% experienced a limited recovery with neurological sequelae and only 50% achieved full recovery [7]. Nevertheless, encephalitis was early ruled out in our patients based on the absence of neurological deficits, diminished level of consciousness or abnormalities in brain imaging techniques.

Regarding the spectrum of VZV-CNS involvement, it is noteworthy the absence of meningeal symptoms and inflammatory parameters in CSF in Patient #2 despite the presence of VZV-DNA. Pleocytosis and/or VZV-DNA in CSF have been reported in up to 61% of immunocompetent patients with HZ and no neurological symptoms but cephalea, suggesting a high prevalence of subclinical meningitis. In this population, CSF abnormalities were not associated to a worse prognosis [8]. However, the prevalence and outcomes of subclinical meningitis in immunocompromised patients with HZ have not been established yet, so it could be an under-recognized condition.

In summary, as prevalence and prognosis of VZV-meningitis in SOT recipients with disseminated HZ remains unclear, it might be reasonable to have a low threshold to perform lumbar puncture in this clinical scenario. Early initiation of intravenous antiviral treatment should also be considered until CNS involvement has been ruled out. Rapid diagnostic tools such as meningitis multiplex PCR test in CSF could be very helpful in this scenario.

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None to declare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

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Letter to the Editor

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Cerebellious abscesses caused by *Nocardia farcinica* in an immunocompromised patient

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Sir,

Nocardia farcinica is a Gram-positive aerobic bacillus that can form branched pseudohyphae [1]. Culture in non-selective media requires 48-72 hours of incubation for visualization of colonies, which present a chalky white or orange appearance, with a slightly cottony appearance due to abundant aerial filaments [2]. Like other species of *Nocardia*, it is characterized by being present in the soil and can be transmitted to man by direct inhalation or by contaminated particles. In 39% of hospitalized patients, the infection commonly manifests as pulmonary disease, although the lesions are not always easily detectable. It is estimated that 9% of *Nocardia* infections lead to a brain abscess, with *N. farcinica* being the most frequent specie [3].

82-year-old female patient who describes cervical pain radiating to occipital area, dysarthria, general weakness and drowsiness to mild stimuli is initially admitted to our Emergency Department. The patient presented history of high blood pressure, dyslipidemia, hearing loss and with a recent temporal arteritis diagnosis. Currently under oral treatment with valsartan 80 mg/day, acetylsalicylic acid 100mg/day, prednisone 30mg/day and methotrexate 2.5mg/week.

On physical examination, the pain worsens with cervical mobilization. Neck stiffness was not observed. Preliminary laboratory evaluation showed CRP of 1.9 mg/L, leukocytes of 9.79x109/L and hematocrit of 30%, with no other findings of interest. The emergency evaluation concluded with a chest x-ray with no abnormal findings. The patient required hospital admission for brain magnetic resonance imaging (MRI). This study revealed the presence of multiple pseudonodular images of cystic appearance with peripheral gadolinium uptake in the posterior fossa, significant diffusion restriction, and slight mass effect and perilesional edema (Figure 1).

Suspecting cerebellar abscesses, the patient underwent craniotomy with evacuation of purulent material from differ-

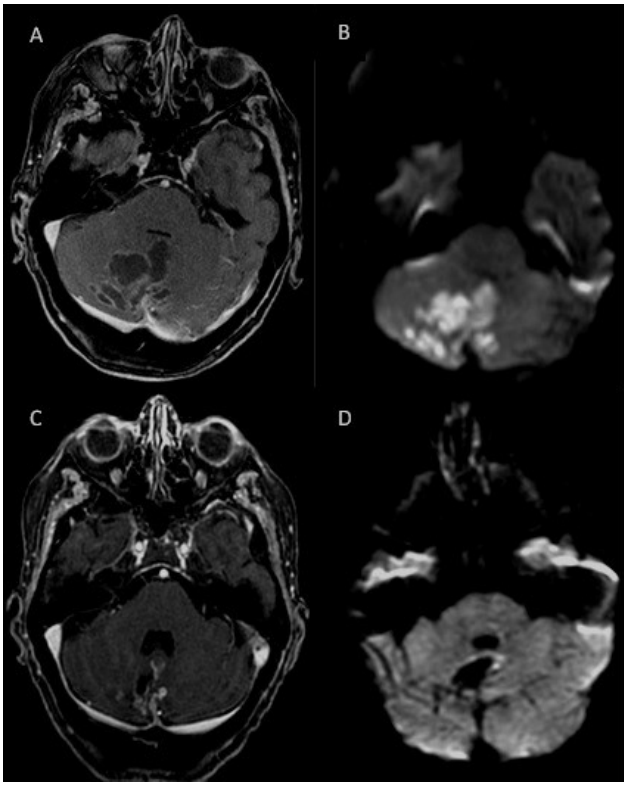

Figure 1 Brain MRI. A) T1 in presurgical axial section with polylobulated peripheral uptake with contrast. B) sequence of diffusion in presurgical axial section with clear restriction of the abscess. C) T1 postsurgical axial section with minimal contrast uptake. D) postsurgical diffusion sequence with almost total absence of restriction.

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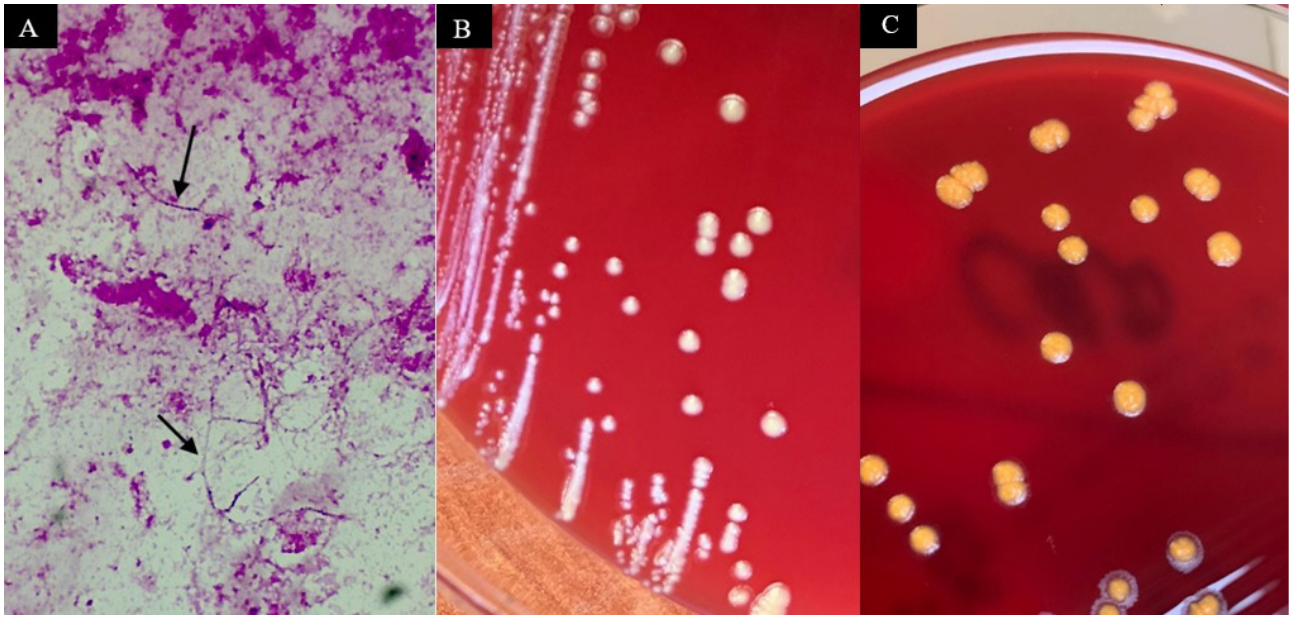

Figure 2 | **A) Gram stain of abscess sample: branched Gram-positive bacilli. B) Abscess cultures after 72 hours and C) 5 days of incubation at 37ºC in aerobic conditions.**

ent cavities and partial excision of the capsule. Samples were collected and sent to the Pathological Anatomy unit and Microbiology laboratory. Given the possibility of an infectious condition, treatment with methotrexate was withdrawn and empirical treatment with cefotaxime, vancomycin, and metronidazole was started.

The anatomopathological study of the drained material ruled out the existence of neoplastic cells. Weak Gram-positive branching bacilli was observed under direct microscopic examination after Gram staining of the abscess sample sent to Microbiology (Figure 2 A). At 72 hours of culture, the growth of small dull white dotted colonies was detected (Figure 2 B) on blood agar that, as the days of incubation passed, acquired a salmon color. The isolate was identified with a high degree of confidence (score = 2.1) using MALDI-TOF technology (Bruker®) as *Nocardia farcinica*. Approximately 75% of *N. farcinica* isolates may be resistant to third-generation cephalosporins [4], so intravenous treatment with cotrimoxazole 800/160mg/8h and amikacin 1g/24h was decided until the sensitivity study was obtained. antibiotic.

The antimicrobial susceptibility study performed by microdilution (SensititreTM RAPMYCOI, Thermo Scientific®) showed MICs, which were interpreted according to CLSI criteria [5] as resistant (ceftriaxone >64 mg/L; imipenem 16 mg/L; ciprofloxacin >4 mg/L) or susceptible (amikacin <1 mg/L; linezolid 2 mg/L; cotrimoxazole 38/2 mg/L).

Twelve days after intervention, neurologic examination was within normal limits overall, with the patient remaining conscious with no additional neurological changes. Hospital discharge was decided to continue with outpatient follow-up and oral treatment with cotrimoxazole 800/160 mg (every 12 h) for 12 months.

Cerebral nocardiosis can occur even in immunocompetent patients, but the highest incidence occurs in immunocompromised patients, such as those treated with corticosteroids or transplant patients, being potentially fatal despite the use of antibiotics and abscess drainage [6]. In recent years, the mortality rate for *N. farcinica* in disseminated infection is estimated at around 39% [7].

The combination of abscess evacuation by craniotomy and administration of antibiotics, being cotrimoxazole the drug of choice, gives very good results for patients with *Nocardia* brain abscess. However, antibiotics must be adjusted according to the sensitivity profiles tested [8], even though a high susceptibility of *Nocardia farcinica* to cotrimoxazole, amikacin, and linezolid has been reported in Spain [4], resistance to cotrimoxazole close to 54% has been documented in other countries [9].

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None to declare

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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