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Secretaría técnica
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
28040 Madrid
revista@seq.es
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Publicidad y Suscripciones
Sociedad Española de Quimioterapia
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
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Atención al cliente
Teléfono 91 394 15 12
Correo electrónico
info@seq.es

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Sumario

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Sumario

REVISTA ESPAÑOLA DE Quimioterapia

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Cartas al Director

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Biomarkers of fungal infection: Expert opinion on the current situation

[1]Microbiología Clínica-Enfermedades Infecciosas. Hospital General Universitario Gregorio Marañón. Madrid. Spain
[2]Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain.
[3]CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058).
[4]Departamento de Medicina. Facultad de Medicina. Universidad Complutense de Madrid. Spain.
[5]Servicio de Enfermedades Infecciosas. Hospital Universitari Vall d'Hebron. Barcelona. Spain.
[6]REIPI (RD16/0016/0003)
[7]Servicio de Microbiología. Hospital La Paz. Madrid. Spain
[8]Servicio de Unidad Clínica de Cuidados Intensivos. Hospital Virgen Macarena. Sevilla. Spain
[9]Servicio de Enfermedades Infecciosas. Hospital La Fe. Valencia. Spain.
[10]Chief Microbiology Department, Policlínico Gemelli, Catholic University. Rome. Italy.

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ABSTRACT

The introduction of non-culture-based diagnostic techniques is revolutionizing the world of microbiological diagnosis and infection assessment. Fungi are no exception, and the introduction of biomarkers has opened up enormous expectations for better management of these entities. Biomarkers are diverse, their targets are also diverse and their evaluation has been done preferably in an individualized use and with deficient designs. Less is known about the value of the combined use of biomarkers and the impact of the negativity of two or more biomarkers on antifungal treatment decisions has been poorly studied. Given the paucity of prospective, randomized and definitive studies, we have convened experts from different fields, with an interest in invasive fungal infections, to answer some questions about the current relevant use of fungal biomarkers. This document summarizes the answers of these experts to the different questions.

Key words: Invasive fungal infections, Intensive Care, Critical Care, Candidemia, Invasive candidiasis, invasive aspergillosis, fungal biomarkers, CAGTA, 1-3ß-D-Glucan, Mannan, Anti-Mannan, T2Candida, Galactomannan, antifungal stewardship

Correspondence:
Emilio Bouza MD, PhD
Instituto de Investigación Sanitaria Gregorio Marañón
Servicio de Microbiología Clínica y E. Infecciosas
C/ Dr. Esquerdo, 46
28007 Madrid, Spain
Phone: +34- 91- 586 84 53/Fax: +34- 91- 504 49 06
E-mail: emilio.bouza@gmail.com

Alternative corresponding author
Patricia Muñoz, MD, PhD
Servicio de Microbiología Clínica y Enfermedades Infecciosas
Hospital General Universitario Gregorio Marañón
C/ Dr. Esquerdo, 46
28007 Madrid, Spain
Phone: +34- 91- 586 84 52/Fax: +34- 91- 504 49 06
E-mail: pmunoz@micro.hggm.es

Biomarcadores de infección fúngica: Opinión de expertos sobre la situación actual

RESUMEN

La introducción de técnicas de diagnóstico no basadas en cultivo está revolucionando el mundo del diagnóstico microbiológico y de la aproximación a las infecciones. Los hongos no son una excepción, y la introducción de biomarcadores ha abierto enormes expectativas para una mejor manejo de estas enfermedades. Hay diversos biomarcadores cuyo significado es también diverso pero su evaluación se ha hecho preferentemente en un uso individual y con estudios con distitnos diseños. Se sabe menos sobre el valor de la combinación de biomarcadores y el impacto de la negatividad de dos o más de los mismos en las decisiones de tratamiento antifúngico ha sido poco estudiado. Dada la escasez de datos prospectivos, en estudios aleatorizados y definitivos, hemos convocado a expertos de diferentes campos con un interés en las infecciones micóticas invasivas, para responder a algunas preguntas sobre el uso actual y relevante de los biomarcadores fúngicos. Este documento resume las respuestas del grupo de expertos a las preguntas que se les formularon sobre el tema.

Palabras clave: Infección fúngica invasora, Cuidados intensivos, Cuidados críticos, Candidemia, Candidiasis invasora, Aspergilosis invasora, biomarcadores fúngicos, CAGTA, 1-3ß-D-Glucano, Manano, Anti-Manano, T2Candida, Galactomanano, política de antifúngicos

INTRODUCTION

Invasive Fungal Infection (IFI) is becoming increasingly important due to a series of circumstances, including the growth of a population with multiple risk factors and immunosuppressed, in which the control of bacterial infections is more effective. Exposure to both endogenous and exogenous fungi is favored by hospitalization and procedures that injure cutaneous-mucous barriers. Finally, the availability of effective

antifungal agents determines the need for rapid and accurate diagnosis.

Culture-based diagnostic media have a recognized and clear role in the diagnosis of invasive mycosis but their deficiencies are also known, particularly in sensitivity and also in speed.

Therefore, it is essential to implement the diagnosis of invasive mycosis with non-culture-based techniques among which biomarkers are already an essential part. However, the position of biomarkers of IFIs in everyday clinical use is far from uniform in all hospitals, the performance of some techniques is under discussion, their interpretation is not always simple and the existing bibliography is sometimes biased for many reasons.

This has led to the convening of a series of experts from the fields of Microbiology, Infectious Diseases and Intensive Care, confronting them with a series of questions that seemed relevant. The open-door meeting took place in Madrid on 23 May 2019 on the occasion of the National Congress of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). This document tries to reflect the main issues discussed, the documentation provided on them and the conclusions that were agreed by the group.

The final document, after having been edited and revised, has been approved by all the participants and represents the opinion of all of them and not necessarily of the institutions to which they belong.

MATERIAL AND METHODS

The questions were chosen by the coordinators and accepted by all the speakers. The document, edited in a first draft has been sent to all co-authors for their corrections and amendments. The final document has been reviewed and approved by all authors.

Next, we will review the questions posed, the arguments provided and the conclusions reached in each of them.

QUESTION 1. Could the importance of invasive fungal infection (IFI) in Spain be quantified? What proportion of it is confirmed by culture?

Dr. Benito Almirante

Background:

Rodríguez-Tudela et al attempted to estimate the incidence of IFIs in Spain in a 2015 publication [1]. They estimated that approximately 9.52 episodes of invasive candidiasis (IC) occur per 100,000 inhabitants and that in the case of Invasive Aspergillosis (IA) the figure was 2.75 episodes/100,000 inhabitants. The number of cases of mucormycosis was significantly lower and was estimated at 0.04 episodes per 100,000 inhabitants per year. They also estimated the figures for certain groups of patients and they reported that 4% of all solid organ transplants and 1.6% of all patients with malignant hematological diseases had, at one time or another, an IFI.

Table 1 lists some studies particularly aimed at evaluating the incidence of candidemia in Spain. As can be seen in table 1, the figures per 100,000 inhabitants per year range from 4.3 to 8.1 episodes and the data estimated with the denominator of 1.000 hospital admissions vary between 0.53 and 1.09 episodes.

At the time of detection of the episode of candidemia, patients in Spain were mostly hospitalized (88%) and a third (35%) were admitted to Intensive Care Units (ICUs). The medical and surgical areas represented 28% and 21%, respectively, and the pediatric areas 3%. A miscellany from other places represented only 1% [2].

The three invasive entities caused by *Candida* were candidemia in the absence of organ candidiasis, candidemia associated with organ disease and candidiasis of organs without accompanying candidemia. The difficulties of diagnosis by conventional methods [7, 8] arise because the sensitivity of blood cultures does not exceed 50% and, when available, is often delayed more than 48 hours. In the case of organ IC, there are only positive reliable cultures in approximately 50%. Invasive procedures are frequently required to obtain proper samples but are rarely possible.

Regarding the conventional diagnosis of IA [9, 10] the challenges are not minor. Signs and symptoms are often nonspecific, it is difficult to distinguish colonization from infection, blood cultures are practically always negative and it is also difficult or impossible to perform invasive techniques for obtaining proper samples. The use of non-culture-based biomarkers is therefore indispensable.

Table 1 Studies on the incidence of candidemia in Spain

Reference	Period	N cases	x10^5 inhabitants	x10^4 days of hospital stay	x10^3 hospital admissions
Almirante B, 2005 [3]	2002-03	345	4.3	0.73	0.53
Rodríguez-Hernández MJ, 2011 [4]	2005-06	220	ND	0.8	0.58
Cisterna R, 2010 [5]	2008-09	984	ND	ND	1.09
Pemán J, 2012 [6]	2009-10	1,357	ND	ND	0.92
Puig-Asensio M. CANDIPOP Project, 2013 [2]	2010-11	773	8.1	1.36	0.89

Conclusion:

Invasive infection caused by *Candida* is estimated in Spain at 9.52 episodes per 100,000 inhabitants/year and that caused by *Aspergillus* at 2.75 episodes. Confirmation with culture occurs in less than 50% of cases due to the frequent negativity of blood cultures and the difficulty of obtaining deep samples of ordinarily sterile tissues or fluids.

QUESTION 2. How should "biomarker of fungal infection" be defined? What are the most important ones at this time?

Dr. Benito Almirante

Background:

A biomarker of fungal infection is a "Biological product from the structure of the fungus/yeast, capable of being detected by "unconventional" techniques, allowing (sometimes) an early and/or anticipated diagnosis of an invasive fungal infection" [11].

Most common ones are summarized in table 2 and are, in the case of *Candida*, mannan and anti-mannan, antibodies against *Candida* germinal tubes (CAGTA), 1-3-β-D-glucan (1-3-ßDG), nucleic acids and the T2Candida nanodiagnostic panel. In the case of IA, the most commonly used are: galactomannan (GLM) in serum, BAL or other samples, 1-3-βDG, nucleic acids (serum, blood or other samples) and Aspergillus lateral flow assay (A-LFD) technology [9, 11-13].

Conclusion:

A biomarker of Invasive Fungal Infection is a biological product from the structure of the fungus/yeast that can be detected by non-culture-based techniques. At this time, the most commonly used in the case of *Candida* are mannan and anti-mannan, antibodies against *Candida* germinal tubes (CAGTA), the 1-3-β-D-glucan, the detection of nucleic acids, and the T2Candida nanodiagnostic panel. In the case of Invasive Aspergillosis, galactomannan, 1-3- β-D-glucan, nucleic acids, and *Aspergillus* lateral flow assay (A-LFD) technology are the more common.

QUESTION 3. What is CAGTA and what does it contribute to the diagnosis of invasive candidiasis?

Dr. Julio García Rodríguez

Background:

The anti-micelium antibody detection system for the diagnosis of invasive candidiasis (IC) (CAGTA) is a technique developed at the University of the Basque Country (Spain) and marketed in the form of indirect immunofluorescence [14]. It was originally designed for the detection of antibodies against antigens expressed in the mycelial phase of *Candida albicans* when it is invading tissues. However, it was soon found to be useful for the diagnosis of infections by other *Candida* species. It is a technique that allows to quantify these antibodies and it is commercialized for the diagnosis of IC.

Table 2 Biomarkers of invasive fungal infection of common use

Biomarkers of invasive candidiasis	Biomarkers of invasive aspergillosis
Mannan-Anti-mannan	Galactomannan (Blood, BAL)
CAGTA	*Aspergillus* Lateral Flow Assay
1-3-ß-D- Glucan	1-3-ß-D- Glucan
Nucleic acids	Nucleic acids
Nanodiagnostic T2Candida	

CAGTA: *Candida albicans* germ tube antibody

The CAGTA test, in individualized use, has been evaluated on numerous occasions with different results. In a recent meta-analysis, the authors found an overall sensitivity of 66% with a specificity of 76% [15]. In addition, in some studies, it has been possible to relate a higher antibody titer with a better prognosis in patients admitted to the ICU, so that it could be used as a prognostic marker depending on its kinetics [16].

Due to its limited diagnostic value, it has been attempted to be used in combination with other biomarkers such as 1,3-ßDG, or antibodies and/or mannan antigens. Recently it has also been combined with the T2Candida magnetic resonance system. According to the different studies, the main usefulness of the combination of these biomarkers lies in their high negative predictive value. This implies that when an antifungal treatment is empirically established, the negativity of two of these markers could be sufficient to safely withdraw the treatment [17-19].

Conclusion:

CAGTA is a *Candida* antimicelial antibody detection system, developed in Spain and commercialized in the form of indirect immunofluorescence. Its negativity, when it coincides with that of other biomarkers, may allow the suspension of antifungal treatments initiated on an empirical basis.

QUESTION 4. What are the indications and limitations of the use of Galactomannan (GLM) in a general hospital at the present time?

Dr. Julio García Rodríguez

Background:

After the study published by the group of Duarte et al. [20] in haematological patients with high risk of fungal infection, who received prophylaxis with posaconazole, and later corroborated in patients on prophylactic treatment with micafungin [21], it has been determined the poor role that the detection of GLM alone plays in these populations when used

as a weekly screening for the initiation of early preemptive antifungal therapy. Both groups of researchers have pointed out that in a setting where the prevalence of IA is reduced to less than 2%, the pre-test probability of GLM falls dramatically, as does the positive predictive value. Therefore, any positive in this situation will be more likely to be a false positive than a true value. These false results may lead these patients to other more or less annoying confirmatory diagnostic tests and, on many occasions, to the initiation of nonrequired antifungal treatments. In short, an increase in the risk of iatrogeny and expenditure.

Although these studies currently advise against the use of GLM as a diagnostic anticipation tool in hematological patients undergoing antifungal prophylaxis, the test is still very useful in those situations in which the patient already has a clear clinical suspicion of IA [22]. There are also other circumstances in which this test is very useful, which are summarized below:

Detection in bronchoalveolar lavage (BAL). The latest reviews and meta-analyses have confirmed that detection of GLM in BAL is more sensitive than in serum, both in hematological and non-hematological patients [23, 24].

Extrapulmonary IA. Other situations in which the determination of GLM may be useful is in extrapulmonary forms of IA such as the case of cerebrospinal fluid for cerebral localizations [25] or peritoneal fluid for the diagnosis of peritonitis [26].

Other applications. Recently, GLM has also been considered useful in the follow-up of high-risk patients in hospitals with undergoing works [27], as a prognostic marker of chronic aspergillosis and as a diagnostic test for disseminated fusariosis [27].

Difficulties. However, the format currently marketed by a microtiter plate capture ELISA makes it very difficult to use the test with only one or a few samples. Initially, a latex agglutination for the detection of GLM antigen existed in a commercialized form, which was substituted by the capture ELISA due to the greater analytical sensitivity of the latter. The ELISA method is useful when studying a large number of patients at risk of IA in a systematic way. New formats are now needed to facilitate its use with a single sample. These new systems must be able to quantify the fungal load and be easy to carry out. One model would be the new immunochromatography based on "Lateral Flow", which is a very simple, but difficult to quantify, technique. The new 1-3-ßDG detection test using WAKO turbidimetry could also be a suitable format. Finally, the new monotest using chemiluminescence developed by Vircell, in the absence of a clinical evaluation and published studies, could respond to these new diagnostic needs**.**

Conclusion:

Galactomannan is a useful diagnostic test for the investigation of Invasive Aspergillosis in patients with clinically suggestive conditions. It can be performed not only in blood but also in CSF, bronchoalveolar lavage or peritoneal fluid. Its systematic and periodic use is not recommended in non-symptomatic hematological patients who are receiving antifungal prophylaxis.

QUESTION 5. To whom should a 1-3 β-D-Glucan level be determined?

Dr. Miguel Salavert

Background:

The performance of classical diagnostic tests on patients who are to be, or are undergoing, antifungal treatment is usually limited to patients who fall within the definition of pre-emptive treatment [28]. However, the use of biomarkers can also be useful to identify therapeutic or prophylaxis failures and can help to confirm or rule out disease in patients on empirical or early treatment or help to decide the duration and prognosis of patients with confirmed diagnosis.

The 1-3-βDG is a component of the fungal wall composed mainly of glucose polymers joined by 1-3 glucosidic bonds that form the skeleton of the fungal wall. As the fungus grows, part of this compound is released into the blood, where it can be measured. Beta-glucans are able to activate the blood coagulation cascade of Limulus polyphemus, the North American horseshoe crab [29], which forms the basis of the diagnostic test. It is produced by fungi such as *Aspergillus* sp, *Candida* sp, *Pneumocystis* sp. *Coccidioides* sp, and *Histoplasma* sp. but is not produced in *Cryptococcus* sp and Mucorales.

The positivity of 1-3-ßDG can anticipate by an average of 10 days diagnostic clinical manifestations of invasive fungal infections [30]. In a study conducted by Tissot et al. [31], in patients with intra-abdominal candidiasis without candidemia, 1-3-ßDG became positive an average of 5 days before confirmation of the diagnosis. In addition, severe sepsis and mortality in this study were higher in patients with higher levels and persisted high, rather than falling, in patients with poor progression.

Determination of 1-3-ßDG can produce both false positives and false negatives. Causes of false positivity include hemodialysis with cellulose membranes, exposure of tissues to cotton gauze and other materials that may contain glucans, administration of blood products through filters, and some antimicrobials such as amoxicillin-clavulanic, piperacillin-tazobactam, co-trimoxazole, colistin, cefepime, ertapenem, and others that suggest contamination with fungal fragments during production [32]. In general, in these cases, the positivity of the test disappears quickly after suspension of the antibiotic or dilution of the sample. There are also false positives described in patients with bacteremia, particularly gram-negative bacteremia, but some studies show that a substantial proportion of bacteremic and 1-3-ßDG-positive patients have simultaneously possible, probable or proven mycoses [33]. Therefore, false positives may occur in patients with bacteremia but this is rare, and the presence of an underlying fungal infection or causes of false positivity other than bacteremia should always be suspected. Although *Candida* colonization does not cause false positives, patients with mucositis may have higher levels of 1-3-ßDG [34].

The classical (Fungitell) determination technique (using kinetic ELISA) has important practical limitations in an assistance labora-

tory as it almost never allows "real time" determination due to the need of batching serums for joint processing. It is also a long (aprox. 3 hours) and laborious technique to perform (not suitable for inexperts). Only 10 µl of sample (serum) are used, and the minimum pipetting error can generate important errors in the result (usually false negatives). In the new format of the technique (WAKO/FUJIFILM), based on the detection of 1-3-ßDG by chemiluminescence in MONOTEST format, it allows to analyze sera individually, in much less time (45-90 minutes) and uses more sample volume (70 µl).

Today, there is no doubt that the addition of 1-3-ßDG to a hospital where immunocompromised patients are cared is a necessity, which is reinforced by the incorporation of the new test presentations, easier to do and more functional. The determination of 1-3-ßDG is already included in the most recent diagnostic guidelines for invasive mycoses [35, 36], although the frequency of the determinations is not clearly specified. Frequently, the rhythm has to do with the laboratory's possibilities to perform the test, which is often done in batches, when enough samples have been accumulated to make the test profitable. This causes clinicians to receive the test at an inadequate pace that does not anticipate clinical events and is inefficient. The availability of a test that allows daily performance, without wasted materials and human resources, can change the clinical use of the test and its diagnostic and prognostic effectiveness.

Today, 1-3-βDG can be a powerful tool in an institution as long as it is properly used and interpreted.

Conclusion:

The presence of 1-3-β-D Glucan should be determined in patients with suspected invasive fungal disease, or as a follow-up to confirmed mycoses, provided that the timing of the determinations, data return, and test interpretation are properly applied.

QUESTION 6. What is the value of a positive or negative 1-3- β-D Glucan? What is the value of its evolution?

Dr. Miguel Salavert

Background:

A positive test for 1-3-ßDG, if the causes of false positives mentioned above are excluded, may suggest the presence of an IFI, not yet demonstrated by other methods, discriminates between colonization and infection in obviously colonized patients, reinforces the results of other diagnostic tests and contributes to the performance of predictive scores.

In the meta-analysis of Karageorgopoulos et al. [37] the results of the 1-3-βDG of patients with or without criteria of certainty or probability of IFI, following the criteria of the EORTC, are compared in the analyzed studies, excluding cases of *P. jirovecii* infection. Of the 594 patients who met this condition, in the 16 studies analyzed, the overall sensitivity of the test was 76.8% and its specificity 85.3%. AUCROC was 0.89 and it is concluded that 1-3-BDG is a test with diagnostic precision to differentiate patients with IFI proven or probable from those who do not have it.

Lamoth´s et al. meta-analysis focuses on hematological patients [38] and includes 6 cohort studies totaling 1,771 adults of whom 414 had IFIs (215 tested or probable). They did not detect discrepancies between the various commercially available tests. When the existence of two consecutive positive tests is used as a positive value, the sensitivity and specificity were respectively 50% and 99%. For an estimated prevalence of 10% of IFIs the PPV and NPV were respectively 83.5% and 95%.

In a meta-analysis based exclusively on prospective studies [39], a total of 1,068 patients from 11 studies were examined and the cumulative data obtained were the following, with 95% confidence intervals: Sensitivity 75%, Specificity 87%, Positive likelihood ratio 5.85, Negative likelihood ratio 0.30, diagnostic odds ratio 19.53, and area under the summary receiver operating characteristic curve, of 0.89. This suggests that this is a clinically useful test with a high ability to distinguish between patients with and without IFI that should be used together with other clinical and microbiological data.

The interpretation requires always to exclude the most frequent causes of false positive summarized in table 3 and false negatives summarized in table 4.

In the case of *P. jirovecii* pneumonia (PJP) [40] 14 studies allowed to analyze the result of 1-3-ßDG in 357 cases and 1,723 controls. Cumulative data showed 95% sensitivity and 86% specificity. The positive and negative likelihood ratios were 6.9 and 0.06, respectively. The area under the HSROC curve was 0.965. The serum 1-3-ßDG determination showed excellent sensitivity and very good specificity in the diagnosis of PJP.

Nucci et al [41] have recently provided interesting data on the use of 1-3-ßDG in the diagnosis and prognosis

Table 3	Some causes of false-positive results in the 1-3 ßDG test

- Contamination of laboratory material with glucans.
- Bacteremia due to *Streptococcus* spp. or some Gram-negative bacilli such as *Pseudomonas* spp.
- Contact with surgical sponges and gauzes.
- Hemodialysis patients with cellulose containing filters.
- IV treatment with immunoglobulins, albumin or coagulation factors.
- Antibacterial IV treatment with antibiotics such as amoxicillin-clavulanic or piperacillin-tazobactam.
- Antineoplastic treatments with Lentinane or Polysaccharide k.

Table 4	Some causes of false-negative results in the 1-3-ßDG test

- Hyperpigmented serums (bilirubin, triglycerides).
- Antifungal treatment (prophylaxis, empirical).
- Azithromycin or pentamidine IV.

of disseminated fusariosis. In a group of 13 cases of fusariosis, 12 had at least one positive test and in 11 of them the test was positive before diagnostic confirmation by other methods. Once treatment was started, the evolution of the determination was also interesting. The 1-3-ßDG continued to grow in patients who died within 30 days, while it was maintained or decreased in those who survived more than 1 month.

The determination of 1-3-βDG has also been carried out on material from bronchoalveolar lavages (BAL). In a meta-analysis that included data from 6 studies and 838 patients (138 with proven or probable IFI), the accumulated sensitivity showed marginal efficacy data, that do not allow interpreting these results in isolation [42, 43].

Another aspect to discuss is the value of 1-3-ßDG follow-up in patients already diagnosed with IFIs. The 1-3-ßDG is a good biomarker of IFIs follow-up if the results are brought quickly to the clinician, which may allow the possibility of antifungal change or de-escalation of them. The control of the evolution of the fungal load can also influence the surgical or instrumental decision making and even in some mycoses allow epidemiological follow-up. In this field, however, methodologically correct studies are needed before clear conclusions can be drawn. Pini et al [44] have analyzed the prognostic potential of 1-3-ßDG in 253 patients with IFIs who conclude with a positive (177 episodes) or negative (76 episodes) evolution. Using an interpretive algorithm based on two different breakpoints of significance, they were able to predict evolution in 82% of cases.

Conclusion:

Two consecutive positive blood tests for 1-3-ßDG, excluding the most frequent and obvious causes of false positivity, are associated with a high suspicion of invasive fungal infection. Its persistence or elevation in confirmed mycoses in antifungal treatment may be associated with poor prognosis.

QUESTION 7. What value does the simultaneous determination of several biomarkers have in daily clinical practice?

Dr. Patricia Muñoz

Background:

Biomarkers do not provide categorical diagnoses, but are Bayesian parameters, which assign a probability of infection (according to pre and post test probabilities). There are several reasons for using more than one biomarker. For example, when the suspected diagnosis is broad (*Candida*, filamentous fungi, etc.) and the possibilities of detection are to be expanded. With false negatives in mind, several biomarkers are used before suspending an empirically initiated antifungal treatment. On the contrary, and trying to avoid the false positive effect, combinations of biomarkers are used to avoid unnecessary treatments.

Martínez-Jiménez et al. used a combination of *Candida* biomarkers in a group of 100 patients with bacteremia and candidemia including CAGTA, Mannan/Anti-mannan (MN/AMN) and 1-3-ßDG (with different cut-off points) in patients undergoing antifungal treatment. Biomarkers, used one by one, had limited sensitivity and specificity. Conversely, various combinations [45] such as the combination of CAGTA and 1-3-ßDG had, globally, a NPV of 97% for the diagnosis of IC. The best behavior of this combination of tests was observed in ICU patients.

Pini et al. [46] retrospectively studied the presence of CAGTA and 1-3-ßDG in stored serum samples from 29 patients with proven IC and 28 controls (9 with demonstrated bacteremia and 9 with negative blood cultures). The association of the two markers clearly increased the sensitivity and accuracy of the separate tests, with the two tests together achieving the following values: 97% sensitivity, 84% specificity, 78% PPV, 95% NPV, and 84% accuracy.

Another possible combination that has been studied is the combination of 1-3-ßDG and procalcitonin (PCT) [47], in patients admitted to intensive care. The study evaluates the significance of 1-3-ßDG positive with PCT less than 2. The combination gives the following results: sensitivity of 96%, specificity of 60%, PPV of 65% and NPV of 95%.

The combined use of 1-3-ßDG with GLM as early markers of fungal infection was used in a monocentric study that enrolled 270 suspected episodes of IFI, 58 proven or probable IA, 27 proven IC, 11 possible IC, 16 *P. jirovecii* pneumonia (PJP) and 4 episodes of other IFI and 154 non-IFI controls. The combination of 1-3-ßDG and GLM increased sensitivity from 60% to 83% in hematological patients [48].

A recent meta-analysis included 13 studies evaluating combinations of GLM, 1-3-ßDG, and aspergillus-lateral flow device (A-LFD) for the diagnosis of IA [49]. Authors included 1,513 patients. Pooled GLM and 1-3-ßDG combination data showed sensitivity of 49%, specificity of 98%, Positive Likelihood Ratio- PLR 32 (95%CI 5.36-187.37), NLR 0.52 (95%CI 0.32-0.84) and DOR 61.23 (95%CI 6.96-538.90). The combinations clearly increased their diagnostic value.

Conclusion:

The simultaneous combination of two or more biomarkers improves both the sensitivity and the negative predictive value of the tests used separately and is therefore clinically useful.

QUESTION 8. Does the negativity of biomarker combinations allow early suspension of antifungal treatment?

Dr. Patricia Muñoz

Background:

Rouzé et al. [50] studied the impact of a strategy based on the use of biomarkers in the early discontinuation of empirical antifungal treatments in ICU. A total of

110 patients were randomized to an antifungal suspension strategy based on the combined use of 1-3-ßDG, mannan, and anti-mannan in serum on days 0 and + 4, compared to the usual standard, based on clinical practice guidelines and 14 days of treatment. In the biomarker-guided group, treatment was discontinued early in 29 of 54 patients compared with only 1 out of 55 early suspension in the group managed without biomarkers (54% vs 2%, $p < 0.001$). The median duration of antifungal treatment was 6 days versus 13 days, with no further differences in the occurrence of IC or differences in mortality between the two groups.

A cohort of 549 high-risk hematological patients undergoing antifungal prophylaxis were followed with antigenic determination and PCR [51]. The combination of techniques showed great utility in the management of IA, with high sensitivity (98%) and NPV (100%) when both tests were used together, allowing both early treatment and early suspension of antifungals. Biomarkers preceded clinical signs in 85% of cases of proven or probable IA.

The screening of IA is essential to decrease the empirical use of antifungals. A meta-analysis of high-risk patients combining GLM and PCR weekly determination, included 13 studies and 1,670 patients [52]. The study concluded that the negativity of all the tests makes it possible to obviate the need to administer antifungal agents with an NPV of 100%, while the presence of at least 2 positive tests is highly suggestive of active infection with a PPV of 88%.

Conclusion:

The negativity of two or more biomarkers of invasive fungal infection supports the suspension of many empirical treatments and is an essential element of an adequate antifungal use policy, although prospective and well-designed studies are still needed to reinforce this concept.

QUESTION 9. Can biomarkers allow, in the future, the individualization of the duration of antifungal treatment?

Dr. José Garnacho-Montero

Background:

In a study carried out in Spain, and already commented [53], 100 patients at high risk of IFI (63 in the ICU) were selected with empirical antifungal therapy. An IC could be tested in 30% of them. Determinations of CAGTA and 1-3-ßDG were made on days 0, 3 and 5 after starting empirical antifungal therapy. The NPV of the combination of both tests was 97% and among non IC patients, all biomarkers were negative in 31/58 patients (53%) and there were 27 false positive results. False positives were more common in the ICU (51.2%) than in general hospital wards (33.3%).

Posteraro et al. [54], in Massimo Antonelli's group, determined the effect of a 1-3-ßDG use strategy in patients at high risk of IC in an ICU. Out of a total of 198 patients, 63 were 1-3-ßDG positive (cut-off value for BDG positivity >80 pg/mL) at some point (47 with candidemia and 16 with probable IC) and all of them received antifungal treatment (31.8%). In the 135 negative 1-3-ßDG patients, 110 (55.5%) never received antifungal treatment and 25 (13%) received it only initially. Candidemia was only diagnosed in 1 patient who had not received previous antifungal treatment. With this approach, the authors reported that they were able to avoid unnecessary antifungal treatment in approximately 73% of potentially treatable patients and reduce duration in another 20% of cases.

The work of Rouzé et al.[50] who prospectively study the impact of a strategy of rapid suspension of empirically initiated antifungal treatments based on the results of 1-3-ßDG has also been commented on. This is a randomized study comparing a group in which treatment is done according to standard recommendations and another that relies on biomarker results. As already commented, the biomarker-based strategy was basically safe and allowed a very substantial reduction in the unnecessary use of antifungals.

The data have therefore so far focused on the use of biomarkers to suspend theoretically unnecessary treatments. In the case of patients with necessary treatments, we have not found data that would allow the evolution of biomarkers to be used as a strategy to shorten or adjust the duration of treatment either in candidemia without organ candidiasis, or in candidemia with candidiasis of organs, or in the case of candidiasis of organs without accompanying candidemia. The dissociation between time to the negativity of blood cultures and time to the negativity of some biomarkers (T2Candida) allows speculation on their future use [55, 56].

Conclusion:

There are no data that permit to state, at this time, that biomarkers and their evolution can be used to adjust the duration of antifungal treatment in patients with invasive fungal infection.

QUESTION 10. To what extent are biomarkers going to modify the attitude towards invasive candidiasis in Intensive Care Units?

Dr. José Garnacho-Montero

Background:

Invasive fungal infections (IFIs) increase their incidence in ICUs where approximately 80% are caused by *Candida* spp. and 0.3-19% by *Aspergillus* spp.[57]. The problem of IC/candidemia in ICUs in Europe has been recently recalled with data from the EUCANDICU study which included 23 ICUs in 9 European countries. The cumulative incidence was 7 episodes per 1,000 admissions with great variability between centers. Crude mortality at 30 days was 42% [58]. We are, therefore, faced with a problem of enormous severity that requires intervention.

The problems related to IF Is in ICU patients are so complex that they need to be addressed by collaborative groups, as suggested in the recommendations of the European Society of

Intensive Care Medicine (ESICM) and the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [59] and should result in the establishment of a stewardship for the rational use of antifungals specifically focused on ICU patients.

Biomarkers are, and will be, an essential element of a policy of diagnostic anticipation and rational use of antifungals. The combined use of CAGTA and 1-3-ßDG in two consecutive samples of ICU patients in Spain, showed 90 % sensitivity, 42 % specificity and 97 % NPV, also allowing a reasonable discriminatory use between colonization and invasion in patients with severe intra-abdominal diseases [17].

Candida biomarkers such as CAGTA, 1-3-ßDG and others need even more research and studies to demonstrate the clinical impact of their systematic use. Future studies should specifically address the use of different diagnostic and therapeutic strategies in patients with intra-abdominal candidiasis [57].

Finally, it is clear that the availability of biomarkers will not delay empirical treatment and therefore will probably reduce mortality. Biomarkers will permit suspension of treatments if negative, in the relevant clinical context, and avoid the overuse of antifungals with considerable ecological and economic benefits.

Conclusion:

***Candida* biomarkers introduce a new era in Intensive Care Units. They will allow a diagnostic and therapeutic anticipation with the consequent decrease in mortality, an early discontinuation of unnecessary empirical treatments. Biomarkers will represent an excellent contribution to antifungal stewardship**

FINAL REMARK

At the time of finishing the edition of this manuscript, during the month of October 2019, a Guideline of the American Thoracic Society has appeared, referring to the microbiological diagnosis of pulmonary fungal infections that we consider of particular relevance and we recommend to read to the readers of this text [60].

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María Julia Ajejas Bazán[1,2]
Carlos Fuentes Mora[2]

Compliance with preventive measures against malaria of personnel treated in the centre of international vaccination of the Minister of Defence (Spain)

[1]Complutense University. Faculty of Nursing, Physiotherapy and Podiatry. Nursing Department. Madrid. Spain.
[2]Preventive Medicine Institute. Defense Ministry. Madrid. Spain.

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ABSTRACT

Objective. This study evaluated the compliance with preventive measures against malaria of the personnel treated in the Spanish Defence International Vaccination Centre (CVI).

Material and methods. A retrospective study was conducted from November to December 2017. The population was 534 individuals. All were treated in CVI, prior to their deployment on endemic areas of malaria, with prevention measures type C and D. A questionnaire of 23 items was elaborated.

Results. The percentage of response to the questionnaire was 36.9% (n=194), 100% were male. Air conditioner was the most used protection measure 93.8% (IC 95% 90.4-97.2). Only 35.5% (95% CI: 28.8-42.2) of them, showed good adherence to medication. The factors that influenced in the adherence were the country and the length of deployment. It was not established a direct relationship between the occurrence of adverse reactions and low adherence to treatment.

Conclusions. The general protection measures against malaria were met in a high percentage, whilst the use of chemoprophylaxis was very low. These epidemiological data allowed us to know the validity of the health education that is provided in the traveller's care consultation. It also allowed being aware of the possibilities of infection and import of malaria by personnel of the Spanish Armed Forces. The traveller's office will reinforce the importance of taking the adequate chemoprophylaxis trough conferences and informative diptychs.

Keywords: Preventive measures, Malaria, Chemoprevention, Adverse Reactions, Mosquito Vectors

Correspondence:
María Julia Ajejas Bazán.
Complutense University. Faculty of Nursing, Physiotherapy and Podiatry. Nursing Department. Madrid. Spain.
E-mail: majejas@ucm.es.

Cumplimiento de las medidas preventivas contra la malaria, del personal tratado en el centro de vacunación internacional del Ministerio de Defensa (España)

RESUMEN

Objetivo. Este estudio evaluó el cumplimiento de las medidas preventivas contra la malaria por parte del personal tratado en el Centro de Vacunación Internacional de la Defensa.

Material y métodos. Se realizó un estudio retrospectivo de noviembre a diciembre de 2017. La población era de 534 individuos. Todos fueron tratados en el Centro de Vacunación Internacional, antes de su despliegue en áreas endémicas de malaria, en las que según indicación de la Organización Mundial de la Salud se recomendaba el uso de medidas de prevención tipo C y D. Se elaboró un cuestionario de 23 ítems.

Resultados. El porcentaje de respuesta al cuestionario fue del 36,9% (n = 194), el 100% eran hombres. El aire acondicionado fue la medida de protección más utilizada 93,8% (IC 95% 90,4-97,2). Solo el 35,5% (IC 95%: 28,8-42,2) de ellos, mostraron buena adherencia a la medicación. Los factores que influyeron en la adhesión fueron el país y la duración del despliegue. No se estableció una relación directa entre la aparición de reacciones adversas y la baja adherencia al tratamiento.

Conclusiones. Las medidas generales de protección contra la malaria se cumplieron en un porcentaje elevado, mientras que el uso de quimioprofilaxis fue bajo. Estos datos epidemiológicos nos permitieron conocer la validez de la educación sanitaria que se brinda en la consulta de atención al viajero. También permitió conocer las posibilidades de infección e importación de malaria por parte del personal de las Fuerzas Armadas Españolas. La oficina del viajero reforzará la importancia de una quimioprofilaxis adecuada a través de conferencias y dípticos informativos.

Palabras clave: Medidas preventivas, Quimioprofilaxis, Malaria, reacciones adversas, vector Mosquito

INTRODUCTION

Malaria is a disease caused by a parasite of the genus Plasmodium, transmitted by the female Anopheles mosquito. It is an important cause of morbidity and mortality worldwide, despite being preventable and able to be cured [1, 2]. According to WHO data in 2015, 212 million cases were diagnosed, which, according to estimates, cost 429,000 lives [3]. The intensification of prevention and control measures has resulted in a reduction in malaria mortality rates of more than 60% worldwide, compared to the rates recorded in 2000. Sub-Saharan Africa remains the area reporting a highest number of the global burden. In 2016, the region accounted for 89% of malaria cases and 91% of deaths due to this cause [3, 4]. Military personnel are considered a high risk group, due to their deployment in operations in tropical and subtropical zones, where there is a high risk of malaria transmission and sometimes a low risk perception, little adherence to protection measures and extensive exposure times to arthropod bites [5, 6]. The implemented preventive measures are divided into four groups: general measures (such as the use of long-sleeved clothing and long pants), physical measures (such as the use of air conditioner and mosquito nets), use of insect repellent, and finally, antimalarial chemoprophylaxis [7]. In the traveller's office of the Institute of Preventive Medicine of the Defence, the health advice and the recommended vaccines are prescribed, administered and facilitated according to the area of deployment. Likewise, in relation to antimalarial chemoprophylaxis, Atovaquone-Proguanil is recommended as the first-line drug, as scientific evidence shows less adverse reactions and greater adherence to treatment [8-10]. Among the adverse reactions described by the technical sheet, the most frequent are: headache, abdominal pain and diarrhoea [11]. Currently there are not studies, neither data about the degree of compliance of the measures established in the Spanish Defence International Vaccination Centre (CVI) to protect the personnel from malaria. These circumstances justify the relevance of conducting this study.

The main aim was to know the degree of compliance with the preventive measures against malaria, of the personnel attended in the CVI of the defence. The secondary aims were: (i) to evaluate the extent of compliance with measures to prevent mosquito bites: general measures, physical measures, use of repellent, and to determine the adherence to chemoprophylaxis malaria; (ii) to describe the occurrence of Adverse Drugs Reactions (ADRs) associated with its consumption; (iii) to establish whether there is a relationship between the occurrence of adverse reactions and the low adherence to treatment; and (iv) to establish whether there is a relationship between the duration of chemoprophylaxis and the increase in adverse reactions.

MATERIAL AND METHODS

A retrospective study was conducted from November to December 2017. The population was 534 individuals. All were treated in CVI, prior to their deployment on endemic areas of malaria, with prevention measures type C (Exists risk of transmission of malaria by *Plasmodium falciparum* and chloroquine resistance and sulfadoxine/pyrimethamine, so military personnel had to take general prevention measures against mosquito bites and chemoprophylaxis with atovaquone-proguanil, or doxycycline or mefloquine (the choice is in role of reported side effects and of the contraindications) and type D (There is a risk of malaria due to *P. falciparum*, in combination with multiple resistance to antimalarial medications, so military personnel had to take general prevention measures against mosquito bites and mefloquine or doxycycline or atovaquone-proguanil (select according to pattern of reported resistance, side effects press releases and contraindications) [12]. A questionnaire of 23 items was elaborated.

The inclusion criteria were:

- Military personnel, Guardia Civil and civil personnel assigned to the Ministry of Defense (MOD) that had been treated in the CVI during the period between September 2016 and September 2017.
- Personnel deployed to malaria endemic areas with type C and D prevention measures and Atovaquone-Proguanil as antimalarial chemoprophylaxis.
- Health advice has been received to prevent mosquito bites.
- Age ≥ 18 years.
- Male and female.
- Weight ≥ 40 kg, according to the drug's data sheet, it is not recommended to administer atovaquone-proguanil for people whose body weight is lower than the aforementioned.

The sample size was calculated taking into account a 5% error, a confidence level of 95% and a loss percentage of 15%. A sample of 173 individuals was obtained.

A questionnaire of 23 items was elaborated with an interrogatively and assertively style. The validation of that questionnaire was carried out with the first 20% of responses received. In addition, an item was included, asking their acceptance to participate in the study and their informed consent. The rest were the variables to be measured previously described.

The first week of November 2017 a questionnaire was sent by email to the selected staff, who fulfilled the inclusion criteria. An informative letter explaining the objectives of the study was attached to the mail. Upon receipt, all personal information of the questionnaire was deleted to preserve the anonymity. Two weeks after the initial send of emails, a reminder of participation was sent. After four weeks of the initial send of emails, the inclusion of questionnaires in the database was completed.

Statistical analysis. It was described by absolute and relative frequencies. To assess whether there was a statistically significant association ($p < 0.05$) of the dependent variable with each of the independent variables, a bivariate analysis was performed using the Pearson Chi-Squared Test. The corresponding confidence interval (ICs 95%) was calculated. A

multivariate analysis was carried out to determine which variables contributed to adherence to preventive measures. The treatment of the data was tabulated and analysed using the statistical package SPSS 21.0 for Windows.

Ethics. Regarding the ethical aspects of the investigation, the provisions of current legislation were respected. The project was presented to the Drug Research Ethics Committee (CEIm) of the Central de la Defensa Hospital (reference 64/17), where it was certified that the study followed the requirements and ethical postulates. Likewise, the data was treated confidentially in accordance with Spanish law (Organic Law 15/1999, of December 13, Personal Data Protection).

Table 1 **Degree of compliance with individual protection measures**

	Degree of compliance		
	n (%)	IC 95 %	p
Air conditioner	182 (93.8)	(90.4-97.2)	0.058
Mosquito screens on windows	108 (56.0)	(49.0-63.0)	0.025
Mosquito nets for bed	67 (34.0)	(27.3-40.7)	0.039
Use of insect repellent	168 (85.8)	(80.9-90.7)	0.098
Chemoprophylaxis	37 (19.0)	(13.5-24.5)	0.076

RESULTS

The study population were 534 individuals, 489 (91.6%) were male and 45 (8.4%) female. 10.6 % had ≤10 years of active time, 18.2% between 11-20 years, 29.8% between 21-30 years and 41.4%> of 30 years. About 1.7 % of the total referred to have completed only Level 1/2 education, 42.2 % A-level education and 56.1 % Higher Education. In relation with their branches, 30.2% belonged to the Army, 15.5% to the Air Forces, 4.9% to the Navy, 8.4% to the MOD, 39.1% to the Guardia Civil and 1.9% to the UME and civil personnel assigned to the MOD. A 4.9 % reported having been deployed to Somalia, 2.8 % to Central African Republic, 5.4 % to Mauritania, 29.2 % to Mali, 10.3 % to Gabon, 11.8 % to Djibouti, 21.3 % to Dakar, 9.0 % to Afghanistan and others 5.3%. Of the total, 28.2 % were deployed < 1 month, 48.1% between 1 and < 6 months, 15.4% 6 months and 8.3% > of 6 months. In addition, 71.6 % reported not taking any medication. All of them were treated at the CVI between September 1, 2016 and September 30, 2017. Everyone travelled to an endemic area of malaria, where the WHO recommends type C and D prevention measures.

A 36.9% response to the questionnaire provided was obtained (n = 194), 100% were male (none female were included), and 7.2% had ≤10 years of active time, 23.2% between 11-20 years, 27.8% between 21-30 years and 41.8%> of 30 years (increased the percentage of individuals between 11-20 years compared to the population, decreasing those who had less active time). About 2.6% of the total referred to have completed only Level 1/2 education, 37.1% A level education and 60.3% Higher Education (Samples studies level were similar to the population). In relation with their branches, 22.2% belonged to the Army, 17.5% to the Air Forces, 5.2% to the Navy, 7.7% to the MOD, 45.9% to the Guardia Civil and 1.5% to the UME and civil personnel assigned to the MOD (participated more Guardia Civil regarding the population). A 5.7% reported having been deployed to Somalia, 2.1% to Central African Republic, 4.6% to Mauritania, 28.9% to Mali, 11.3% to Gabon, 9.8% to Djibouti, 18.0% to Dakar, 8.2% to Afghanistan and others 11.3% (the percentage of people who participated in the different countries was similar in the sample and population). Of the total, 26.0% were deployed < 1 month, 40.2% between 1 and < 6 months, 17.7% 6 months and 16.1% > of 6 months. In addition, 68.9% reported not taking any medication. All the results presented in this study referred to the personnel who responded to the questionnaire. A bivariate analysis was also carried out between the personnel who answered the questionnaire and those who did not, finding no statistically significant association (p = 0.136).

In relation to the degree of compliance with personal preventive measures, air conditioner was the most used protection measure 93.8% (IC 95% 90.4-97.2) (table 1).

One influential factor was the educational level. Staff with higher education made more use of air conditioner (56.1%) than those with a lower level (2.6%). The same happened with the use of mosquito screens on windows, with a bigger use in those with higher education (33.7%) compared to personnel with Level 1/2 education (2.6%). Regarding the use of mosquito nets for beds, it was (22.3%) for personnel with higher education, compared with (0.0%) of personnel with Level 1/2 education. Being statistically significant the association (p = 0.036, p = 0.02 and p = 0.027 respectively) (table 2).

The Guardia Civil was the most numerous group that made use of air conditioner (42.8%), followed by the Army (20.6%). It was also the Guardia Civil the bigger group using mosquito screens in windows (28.9%) and mosquito nets for beds (15.7%). Statistically, there was only a significant association in the use of mosquito screens for windows and mosquito nets for beds (p = 0.02, p = 0.035 respectively) (table 2).

The country of deployment, where physical measures of protection were most used, was Mali (air conditioner 27.8%, screen for windows 28.0% and net for beds 22.3%); there is only a statistically significant association in the use of nets for windows and beds (p< 0.01) (table 2).

In relation to the length of the deployment, the shorter the stay, the more they used mosquito screens for windows (<1 month (18.1%) > 6 months (12.8%)) and beds (<1 month (9.4%)> 6 months (8.9%)). A statistically significant association was found in both cases (p = 0.01, p = 0.027 respectively) (table 2).

The country where the insect repellent was most used was Mali (26.9%) and the country with a higher antimalarial chem-

Table 2 List of factors were influenced on the degree of compliance with the measures of individual protection.

		Total n (%)	Air conditioner Yes			p-value	Mosquito screens on window Yes			p-value	Mosquito net for bed Yes			p-value	Use of insect repellent Yes			p-value	Use of chemoprophylaxis Yes			p-value
			n	%	95 % IC		n	%	95 % IC		n	%	IC 95 %		n	%	95 % IC		n	%	95 % IC	
Active Service	≤ 10 years	14 (7.2)	14	7.2	(3.4-10.6)	0.921	7	4.1	(1.3-6.9)	0.239	4	2.0	(0.0-4.0)	0.171	12	7.6	(3.9-11.3)	0.561	3	1.5	(0.0-3.2)	0.874
	11-20 years	45 (23.2)	43	22.2	(16.2-27.8)		28	13.0	(8.3-17.7)		20	9.6	(5.5-13.7)		38	23.4	(19.4-27.4)		7	2.6	(0.4-4.8)	
	21-30 years	54 (27.8)	50	25.8	(19.6-32.0)		37	18.1	(12.7-23.5)		20	10.2	(7.4-13.0)		49	27.9	(21.6-34.2)		11	4.1	(1.3-6.9)	
	> 30 years	81 (41.8)	75	38.7	(31.8-45.6)		43	20.7	(15.0-26.4)		25	12.2	(9.1-15.3)		74	41.1	(34.2-48.0)		23	10.8	(6.4-15.2)	
Education Level	Level 1/2 education	5 (2.6)	5	2.6	(0.4-4.8)	0.036	5	2.6	(0.4-4.8)	0.023	0	(0.0)	(0.0-0.0)	0.013	3	1.5	(0.0-3.2)	0.086	2	1.0	(0.0-2.4)	0.861
	A-level education	72 (37.1)	68	35.1	(28.4-41.8)		39	19.7	(14.1-25.3)		20	11.7	(7.2-16.2)		62	33.0	(26.4-39.6)		10	5.6	(2.4-8.8)	
	Higher Education	117 (60.3)	109	56.2	(49.2-63.2)		65	33.7	(27.0-40.4)		44	22.3	(18.4-26.2)		101	51.3	(44.3-58.3)		24	12.3	(7.7-16.9)	
Force belonging	Army	43 (22.2)	40	20.6	(14.9-26.3)	0.071	33	17.1	(11.8-22.4)	0.017	21	10.7	(7.8-13.6)	0.045	34	17.3	(12.0-22.6)	0.342	8	4.1	(1.3-6.9)	0.783
	Air Forces	34 (17.5)	32	16.5	(11.3-21.7)		12	6.2	(2.8-9.6)		5	2.5	(1.0-4.0)		32	16.8	(11.5-22.1)		6	3.1	(0.7-5.5)	
	Navy	10 (5.2)	10	5.2	(2.1-8.3)		3	1.6	(0.0-3.4)		2	1.0	(0.0-2.4)		10	5.1	(2.0-8.2)		1	0.5	(0.0-1.5)	
	To the MOD	15 (7.7)	14	7.2	(3.6-10.8)		10	4.7	(1.7-7.7)		7	3.6	(1.0-6.2)		12	6.6	(3.1-10.1)		4	2.6	(0.4-4.8)	
	Guardia Civil	89 (45.9)	83	42.8	(35.8-49.8)		53	25.9	(19.7-32.1)		31	15.7	(12.3-19.1)		76	38.6	(31.7-45.5)		17	8.7	(4.7-12.7)	
	UME	1 (0.5)	1	0.5	(0.0-1.5)		1	0.5	(0.0-1.5)		1	0.5	(0.0-1.5)		1	0.5	(0.0-1.5)		0	0.0	(0.0-0.0)	
	Civil personnel assigned to the MOD	2 (1.0)	2	1.0	(0.0-2.4)		0	0.0	(0.0-0.0)		0	0.0	(0.0-0.0)		2	1.0	(0.0-2.4)		0	0.0	(0.0-0.0)	
Country of deployment	Somalia	11 (5.7)	11	5.7	(2.4-9.0)	0.648	11	3.1	(0.7-5.5)	0.041	0	0.0	(0.0-0.0)	0.046	7	3.6	(1.0-6.2)	0.001	4	2.1	(0.1-4.1)	0.003
	Central African Republic	4 (2.1)	4	2.1	(0.1-4.1)		4	2.1	(0.1-4.1)		4	2.0	(0.0-4.0)		2	1.0	(0.0-2.4)		0	0.0	(0.0-0.0)	
	Mauritania	9 (4.6)	7	3.6	(1.0-6.2)		7	3.6	(1.0-6.2)		4	2.0	(0.0-4.0)		9	4.6	(2.2-6.6)		4	2.1	(0.1-4.1)	
	Mali	56 (28.9)	54	27.8	(21.5-34.1)		54	28.0	(21.7-34.3)		44	22.3	(18.4-26.2)		52	26.9	(20.7-33.1)		7	4.1	(1.3-6.9)	
	Gabon	22 (11.3)	22	11.3	(6.8-15.8)		9	4.7	(1.7-7.7)		0	0.0	(0.0-0.0)		20	10.2	(7.4-13.0)		0	0.0	(0.0-0.0)	
	Djibouti	19 (9,8)	19	9.8	(5.6-14.0)		4	2.1	(0.1-4.1)		0	0.0	(0.0-0.0)		17	8.6	(4.7-12.5)		3	1.5	(0.0-3.2)	
	Dakar	35 (18.0)	33	17.0	(11.7-22.3)		10	5.2	(2.1-8.3)		7	4.6	(2.2-6.6)		35	18.8	(13.3-24.3)		10	5.1	(2.0-8.2)	
	Afghanistan	16 (8.2)	14	7.2	(3.6-10.8)		10	5.2	(2.1-8.3)		0	0.0	(0.0-0.0)		6	3.0	(1.4-4.6)		6	3.1	(0.7-5.5)	
	Other	22 (11.3)	18	9.3	(5.2-13.4)		4	2.1	(0.1-4.1)		6	3.0	(1.4-4.6)		18	9.1	(5.1-13.1)		2	1.0	(0.0-2.4)	
Trip duration	< 1 month	50 (26.0)	46	23.8	(17.8-29.8)	0.151	37	18.1	(12.7-23.5)	0.011	19	9.4	(5.3-13.5)	0.023	46	24.0	(0.2-4.6)	0.041	2	1.1	(0.0-2.6)	0.036
	> 1-4 months	79 (40.2)	77	38.6	(31.7-45.5)		28	14.9	(9.9-19.9)		20	10.4	(6.1-14.7)		75	38.0	(31.2-44.8)		12	6.3	(2.9-9.7)	
	> 4-6 months	34 (17.7)	30	15.9	(10.8-21.0)		24	11.7	(7.2-16.2)		12	6.3	(4.0-8.6)		20	10.4	(6.1-14.7)		12	6.3	(2.9-9.7)	
	> 6 months	31 (16.1)	29	15.3	(10.2-20.4)		24	12.8	(8.1-17.5)		17	8.9	(6.2-11.6)		25	13.0	(8.3-17.7)		8	4.2	(1.4-7.0)	

Table 3 **Multivariate analysis of temporal trends and associated factors.**

		Mosquito screens on window		Mosquito net for bed	
		OR	(IC 95 %)	OR	(IC 95 %)
Active Service	≤ 10 years	1.87	(1.68-1.99)	1.62	(1.55-1.69)
	11-20 years	1.4	(1.21-1.60)	1.38	(1.30-1.46)
	21-30 years	1.01	(0.99-1.03)	1.05	(0.97-1.09)
	> 30 years	1		1	
Education Level	Level 1/2 education	1.24	(1.07-1.42)	1.37	(1.21-1.54)
	A-level education	1.17	(1.05-1.30)	1.11	(1.03-1.20)
	Higher Education	1		1	
Force Belonging	Army	1.49	(1.34-1.64)	1.43	(1.33-1.53)
	Air Forces	1.42	(1.36-1.59)	1.41	(1.38-1.57)
	Navy	1.36	(1.21-1.52)	1.31	(1.29-1.33)
	To the MOD	1.28	(1.05-1.35)	1.27	(1.11-1.35)
	Civil Personnel	1.23	(1.11-1.35)	1.2	(1.18-1.22)
	UME	1.22	(1.09-1.39)	1.1	(1.09-1.11)
	Guardia Civil	1		1	
Trip duration	< 1 month	1.36	(1.21-1.52)	1.68	(1.58-1.78)
	> 1-4 months	1.22	(1.09-1.39)	1.32	(1.22-1.42)
	> 4-6 months	1.01	(0.92-1.1)	1.11	(1.01-1.2)
	> 6 months	1		1	

oprophylaxis was Dakar (5.1%); there are statistically significant association in both cases (p< 0.01).

In relation to the length of the deployment, the period in which the insect repellent was most used, was the one that ranged between > 1 month and 4 months (38.0%) and regarding the antimalarial chemoprophylaxis there were two periods with a significant impact, those who ranged between > 1 month and 4 months and between > 4 months and 6 months (6.3% in both cases), there are statistically significant associations (p < 0.01, p = 0.03 respectively).

In order to measure the adherence to the use of antimalarial chemoprophylaxis it was used the "Morisky- Green Test"[13, 14]. Of the total of individuals who made up the sample, only 35.5% (95% CI: 28.8-42.2) showed good adherence to medication consumption, compared to 64.5% (95% CI: 57.8-71.2), which did not. About the different factors that could influence the good adherence or not to chemoprophylaxis, the only statistically significant association was the country of deployment. The personnel that travelled to Dakar presented a higher percentage of adherence (10.7% CI95%: 6.4-15.0) (p = 0.008). Likewise, a significant association was found between the personnel who consumed another type of medication with a good adherence to chemoprophylaxis (15.2% CI 95%: 10.2-20.2) (p = 0.023).

In relation to the appearance of ADRs, 31.1% of the staff reported the presence of some of them, 63.7% did not mention anything and 5.2% answered do not know, no answer (DK/NO). Of the total of individuals who reported having suffered some ADR, the most frequent was diarrhoea with abdominal pain (33.9%) followed by headache (10.1%). A 69.6% declared that despite having suffered ADRs, they did not stop taking their chemoprophylaxis, compared to the 9.4% who said they did. Of the 30.5% who presented ADRs, 4.2% received hospital healthcare, finding association only with the trip duration, the longer the stay the greater the appearance of ADRs.

No relationship was established between the occurrence of adverse reactions and the low adherence to treatment, because no statistically significant association was found, despite the fact that the personnel with low adherence presented a higher number of ADRs (66.2%) than those who did not (p=0.981). Personnel with reactions maintained good adherence (33.8%).

Regarding the last objective, there was no relationship between the duration of the chemoprophylaxis and the increase in adverse reactions. The highest percentage of ADRs was presented by personnel who remained deployed between > 1 month and 4 months (14.7%) compared to 4.2% of those who were deployed for more than 6 months, with a statistically significant association (p = 0.004).

Regarding the use of mosquito screens on window and mosquito net for bed, the variables significantly associated with a lower probability of adhesion are shown in table 3. Those professionals with less active service were 1.87 (1.68-1.99) more likely not to use mosquito screens on window and mosquito net for bed 1.62 (1.55-1.69). Also, those with a lower level of education were more likely not to use mosquito screens on window 1.24 (1.07-1.42) and mosquito net for bed 1.37 (1.21-1.54). Army personnel were the most likely to not use mosquito screens on window 1.49 (1.34-1.64) and mosquito net for bed 1.43 (1.33-1.53). To conclude the shorter trip duration, more likely not to use the mosquito screens on window 1.36 ((1.21-1.52) and mosquito net for bed 1.68 (1.58-1.78).

DISCUSSION

The percentage of response was 36.9%, lower than other studies conducted where it ranged between 100% [14], 83.2% [15] and 74% [16], although similar to another study with 36.2% [17]. The reason could be the place where military personnel carry out their activity, sometimes outside their facilities with a difficult access to Internet. Another alternative method for completing the survey was not contemplated. Maybe in later studies the mobile will be used as a means to answer the survey.

Not many differences were found between the responding group and the one that did not, except sex, perhaps there is no contact with the interviewee, rejection of the same, inability to cooperate (illness, language problems) or schedule difficulties.

In relation to the degree of compliance with the measures of individual protection, the use of air conditioner by the personnel of our Armed Forces was 93.8%, only association being found at level of studies. No bibliography has been found that has studied the use of air conditioner in the rooms, perhaps it was not available in the rooms or they didn't use it as a preventive measure. The intensive use of air conditioner by staff could be triggered by the high temperatures in the deployment areas.

The percentage of use of mosquito screens on windows was 56.0%, differences were found between education level, force belonging, country development a trip duration. Data similar to a study carried out in Saudi Arabia where the percentage was 47.3% [18]; but higher than the results of other studies, where the percentage ranged between 18.0% [15] and 19.7% [19]. The difference in use could be because the meshes were installed both in hotels and military bases where the staff of this study was housed and the rest of the results referred to non-military facilities.

In the present study, the mosquito net for beds was used by 34.0% of the personnel, differences were found between education level, force belonging, country development a trip duration. Similar data was found in another article carried out in Tibet, 35.0% [16], but other studies have lower percentages 19.7% [20], 18.14% [14] and 2.2% [21]. The use could be due to the health advice received in the traveller's office and/or the use of facilities with a prior installation of nets.

An 85.8% used insect repellent on a regular basis, differences were found between education level, country development a trip duration. Our results were higher than other studies were the percentages ranged from 41.9% [17] to 32.2% [21]. There were also other studies with even lower percentages, oscillating between 16.8% (2002), 15.0% [20], 11.2% (2007) [15] and 7.24% [14]. This intensive use was perhaps a consequence of the insistence in the importance of this measure to avoid the bite of insects by the medical personnel and the health advice provided in the traveller's office.

Only 19.0% of personnel reported the use of chemoprophylaxis, differences were found between country development and a trip duration. A very low figure if we compare it with other studies where 82.1% [15] took antimalarial tablets. The reason for this behaviour could be related to the appearance of ADRs. The staff used more chemoprophylaxis depending the country of deployment, especially if they were African countries and if the length of the deployment was between 1 and 6 months. It could be that longer periods favour the feeling of immunity in the staff or the fear of adverse reactions. On the other hand, it could be than the staff believes that, a short stay, could reduce or avoid the probability of mosquitoes' bite.

A 31.1% showed the presence of ADRs, in the present study. Data very similar to others where the percentage was 32.2% [21], 24% [23] or 25% [15] corresponding to those reflected in the drug's technical data sheet [12]. Once established that it was not the appearance of ADRs one of the causes of low staff adherence, perhaps the reduction was related to the intensive use of repellents. The general protection measures against malaria were met in high percentage, while the use of chemoprophylaxis was very low. These epidemiological data allowed us to know the validity of the health education that is provided in the traveller's office care consultation. It also allowed being aware of the possibilities of infection and import of malaria by personnel of the Spanish Armed Forces. The traveller's office will reinforce the importance of taking the adequate chemoprophylaxis trough conferences and informative diptychs.

The most important limitation of this study refers to the sample. Also, another limitation of this study was the low response rate obtained, although higher than the sample size calculated. Likewise, if a sample size calculation had been made with a 5% error rate and a 95% confidence level and an expected loss ratio of 30%, the number of individuals should have been 210 versus 194 that formed the study. Selection through a probabilistic sampling stratified by gender should have included 193 males (194 were included) and 17 females (none were included). There was no female answer data available. Perhaps, most of the personnel who answered did it because they mostly complied with the measures of individual protection, against those who did not comply and were reluctant to answer. The external validity of this study is not very high due to its limitation. To improve adherence to chemoprophylaxis, health education measures should be implemented such as conferences, delivery of leaflets or use of mobile apps.

The personnel protection is essential to safeguard the health of the individual, the group and national public health upon return. Measures of general protection against malaria were met in a high percentage of cases, except the use of antimalarial chemoprophylaxis. The degree of compliance with the use of air conditioner, mosquito screens for windows and insect repellent of our Armed Forces was very high. The use of chemoprophylaxis was very low (19.0 %) nevertheless the staff used more chemoprophylaxis if were deployed in African countries and if the length of the deployment was between 1 and 6 months. Only 31.1% showed the presence of ADRs, but this was not one of the causes of low staff adherence. The health education provided in the traveller's office care consultation is valid but there must be reinforced the importance of taking the adequate chemoprophylaxis. Therefore, it is necessary to change and reorient the current health education.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Desarrollo de modelo experimental animal de peritonitis bacteriana

Omar Montenegro[1]
Soledad Illescas[2]
José Carlos González[2]
David Padilla[3]
Pedro Villarejo[3]
Victor Baladrón[1]
Rocio Galán[4]
Natalia Bejarano[5]
Lucia Medina-Prado[6]
Natalia Villaseca[6]
José Manuel Pérez-Ortiz[6]
José Ramón Muñoz-Rodríguez[6]
Juan Luis Santiago[6]
Francisco Javier Redondo[1]

[1]Servicio de Anestesiología y Reanimación. Hospital General Universitario de Ciudad Real.
[2]Servicio de Microbiología. Hospital General Universitario de Ciudad Real.
[3]Servicio de Cirugía. Hospital General Universitario de Ciudad Real.
[4]Servicio de Oncología. Hospital General Universitario de Ciudad Real.
[5]Servicio de Pediatría. Hospital General Universitario de Ciudad Real.
[6]Unidad de Investigación Traslacional. Hospital General Universitario de Ciudad Real.

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RESUMEN

Objetivo. Desarrollar un modelo de sepsis abdominal en animal de experimentación.

Material y métodos. Se utilizan ratas Sprague-Dawley®, machos de 5 semanas con pesos entre 270-280 g en el momento de la inoculación (N=39). Inicialmente se realiza un estudio piloto (N=9), distribuyéndolas en 3 grupos (3/3/3) con inóculo de 1cc de *Escherichia coli* ATCC 25922 intraperitoneal en concentraciones de 10^8, 10^9 y 10^{10} UFC. En un segundo estudio (N=6) con distribución en dos grupos (3/3) se utilizan 1cc una concentración de *E. coli* 10^{10} UFC que se diluyen en 10 y 15 ml de agua destilada para su inoculación. Por último se inicia un ensayo experimental con aleatorización de 24 ratas en tres grupos de tratamiento tras la infección intraperitoneal: Grupo I con suero fisiológico (N=6), Grupo II con antibiótico (ceftriaxona) (N=9), Grupo III con antibiótico más adyuvante (ceftriaxona más alicina) (N=9). Se realizan muestras microbiológicas de sangre y líquido peritoneal, así como estudio histopatológico de órganos intraperitoneales (hígado, diafragma y peritoneo).

Resultados. Se observa muerte en el 100% de las ratas infectadas con la concentración de *E. coli* 10^{10} UFC con la dilución de 15 ml de agua destilada y sin antibiótico. El hemocultivo y cultivo de líquido peritoneal es positivo a la misma cepa en todas ellas. Se observa la formación de abscesos en la superficie del hígado e infiltración por polimorfonucleares en los tejidos.

Conclusión. Se establece que la dosis letal de *E. coli* es 10^{10} UFC diluida en 15 ml agua destilada en inyección intraperitoneal.

Palabras clave: Sepsis, peritonitis, *Escherichia coli*, ratas

Correspondencia:
Fco Javier Redondo Calvo,
Servicio de Anestesiología y Reanimación. Unidad de Investigación Traslacional.
Hospital General Universitario de Ciudad Real.
C/Obispo General Torija s/n.13005. Ciudad Real. España
Tfno.: 626320968
E-mail: fjredondo@sescam.jccm.es

Development of animal experimental model for bacterial peritonitis

ABSTRACT

Objective. The aim of the study was to develop a model of abdominal sepsis in the experimental animal.

Material and methods. Sprague-Dawley male rats of 5 weeks (N=39) were used. Initially, a pilot study (N = 9) was performed and distributed in 3 groups with 1cc inoculum of *Escherichia coli* ATCC 25922 intraperitoneally at concentrations of 10^8, 10^9 and 10^{10} CFU. Subsequently, concentrations of 10^{10} CFU are used in two groups of 3 rats with dilutions of 10 cc and 15 cc of distilled water respectively. Finally, a randomized trial of 24 rats was started in three treatment groups after intraperitoneal infection: Group I with physiological serum (N = 6), Group II with ceftriaxone (N = 9), Group III with ceftriaxone plus allicin (N = 9). Microbiological samples of blood and peritoneal fluid were made, as well as histopathological study of intraperitoneal organs (liver, diaphragm and peritoneum).

Results. Death of 100% of the rats infected with 10^{10} *E. coli* UFC concentration with the dilution of 15 ml of distilled water and without antibiotic was oberved. The blood culture and peritoneal fluid culture was positive for the same strain in all of them. The formation of abscesses on the liver surface and polymorphonuclear infiltration in tissues were observed.

Conclusion. The lethal dose of *E.coli* is 10^{10} CFU diluted in 15 cc distilled water by intraperitoneal injection

Key words: Sepsis, peritonitis, *Escherichia coli*, rats

INTRODUCCIÓN

A lo largo de la historia se han utilizado animales de experimentación para crear distintos modelos que ayuden a comprender las causas, diagnóstico y tratamiento de enfermedades que afectan al humano y a los propios animales. También han

servido como aporte a la docencia biológica, desarrollo, producción y control de medicamentos y alimentos [1].

En el contexto de la sepsis/shock séptico existen una gran cantidad de modelos animales que intentan replicar la fisiopatología de la sepsis humana. Sin embargo encontramos importantes diferencias entre ambas especies y el desarrollo del proceso séptico normalmente no reproduce las condiciones de la sepsis humana. En primer lugar, la sepsis en humanos es una patología de presentación paulatina e insidiosa y en los animales la sepsis suele ser mucho más aguda [2]. En segundo lugar, la intervención experimental sucede en las etapas tempranas de la sepsis, cuando todavía los niveles de citocinas inflamatorias están elevados y el daño orgánico y vascular es mínimo, a diferencia del ser humano, donde la intervención terapéutica habitualmente se produce cuando la respuesta de las citocinas proinflamatorias está cambiando a anti-inflamatorias y el daño orgánico ya es aparente. En tercer lugar, es habitual que la población susceptible en humanos sea en los extremos de la vida (niños y adultos mayores), en cambio los animales que se utilizan para experimentación son adultos jóvenes sin otras comorbilidades. En cuarto lugar, los animales en la mayoría de modelos no reciben un tratamiento de soporte completo que incluya la ventilación mecánica, fluidoterapia, fármacos inotrópicos, antibioterapia, soporte nutricional enteral o parenteral y terapia renal sustitutiva. Por último, el tiempo transcurrido desde el comienzo de los síntomas hasta el fallo orgánico es mucho más corto en modelos animales, en los que el proceso se concentra en unos pocos días. En humanos el tiempo transcurrido hasta el fallo orgánico suele ser de semanas. Todo esto afecta severamente a la evaluación de las terapias farmacológicas anti sepsis [3]. Y de aquí que no exista un modelo idóneo, cada modelo presenta ventajas y desventajas en función del parámetro que se desea estudiar y el animal de experimentación empleado.

Uno de los modelos de experimentación animal más utilizada es el creado a partir de la inyección, tanto local como sistémica de bacterias vivas, con frecuencia *Escherichia coli* o de productos bacterianos o endotoxinas como los lipopolisacáridos (LPL) [4]. El uso de endotoxinas presenta una gran cantidad de limitaciones en roedores, siendo la principal, la elevada dosis necesaria para producir un estado de shock, que es entre 10 y 100 veces superior a la necesaria en humanos. Por otro lado, existen diferencias en la clínica que la endotoxina induce en roedores y en humano [5, 6].

Otros modelos se generan a partir de la manipulación del intestino y el vertido de contenido fecal a la cavidad peritoneal generando una peritonitis polimicrobiana y como consecuencia una respuesta inflamatoria sistémica.

El procedimiento más ampliamente utilizado para generar un modelo de peritonitis en roedores es la ligadura y punción del ciego (CLP "*cecal ligation and puncture*"). Este modelo es apto para la evaluación de terapias que actúan sobre los cambios fisiopatológicos producidos durante el proceso séptico. Se ha considerado la técnica "gold standard" [7, 8].

Dados los escasos modelos de sepsis reproducibles en la literatura se plantea desarrollar y estandarizar un modelo de sepsis abdominal en animal de experimentación mediante la inoculación de *E. coli* con punción única en cavidad peritoneal.

MATERIAL Y MÉTODOS

Animales de experimentación y condiciones de estudio. Se ha desarrollado un estudio experimental (ensayo terapéutico) de infección intraabdominal donde se utiliza el animal de experimentación rata Sprague-Dawley®, Harlan Laboratories Models SL, macho, 5 semanas y 100-125 g. Tras una semana de aclimatación y previo a la experimentación todos los animales alcanzan pesos entre 270-280 g. Se lleva a cabo en las instalaciones de la Unidad de Investigación Traslacional (UIT) del Hospital General Universitario de Ciudad Real.

Se realiza en idéntico horario, para evitar la posible influencia del ciclo circadiano en los resultados del trabajo. Todos los animales estaban sanos y no recibieron tratamiento previo.

Los animales se mantienen con comida y agua *ad libitum*, con un ciclo 12 horas de luz y 12 horas de oscuridad, y una temperatura ambiente de 22±2ºC con una humedad relativa del aire del 50-70% y con 15-20 renovaciones/hora sin recirculación de aire. Son estabulados conforme al RD 53/2013 y ninguno en solitario, para favorecer el comportamiento grupal de los mismos. Además se mantienen una semana en estas condiciones ambientales, para permitir su aclimatación, antes del inicio del estudio.

Se realiza un marcaje mediante tatuaje permanente en la cola de las ratas, para poder hacer el seguimiento individual del estado de bienestar de cada una de ellas. La localización de los animales y su estabulación se realiza en el animalario la citada Unidad de Investigación Traslacional.

Todos los procedimientos experimentales se realizan de acuerdo con las directrices de la normativa Europea (Directiva 2010/63/EU) de protección de los animales de experimentación y con la española (RD 53/2013). El estudio ha sido aprobado por el Comité Ético de Experimentación Animal y Órgano Habilitado del Hospital General Universitario de Ciudad Real.

Los desechos convencionales y biológicos son retirados y eliminados de forma regular, segura y conforme a las recomendaciones institucionales de riesgos laborales.

Modelo de trabajo animal

Determinación de dosis letal (estudio piloto). Inicialmente se realiza un estudio piloto con (N=9), distribuyéndolas en 3 grupos (3/3/3) con inóculo de 1 ml de *E. coli* ATCC 25922 intraperitoneal en concentraciones de 10^8, 10^9 y 10^{10} UFC. En un segundo estudio (N=6) con distribución en dos grupos (3 / 3) se utilizan 1 ml de *E. coli* 10^{10} UCF siendo diluidas en 10 y 15 ml de agua destilada para su inoculación.

Para la creación del modelo de peritonitis se realiza inyección intraperitoneal a ratas con pesos comprendidos entre 270-280 gramos, previa anestesia con ketamina/xilacina 75/10 mg/kg intraperitoneal (figura 1).

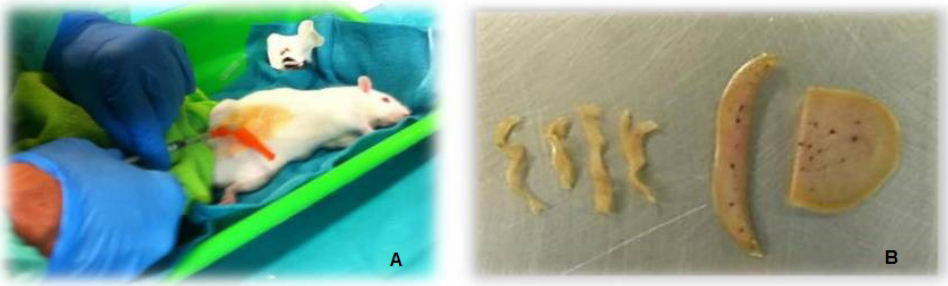

Figura 1 | **Corresponde a la administración de tratamiento inmediatamente después de la inoculación con *E. coli* intraperitoneal en la rata anestesiada (A). Cortes realizados en el hígado para evaluación histopatológica (B).**

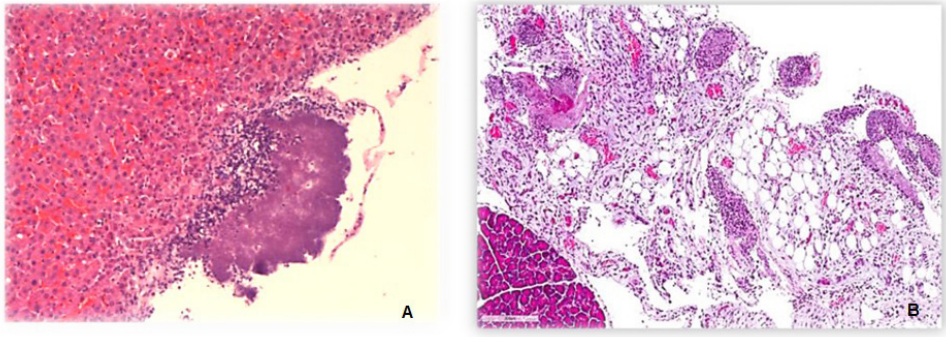

Figura 2 | **Absceso en la superficie del hígado. Infiltración de PMN y colonias bacterianas (A). PMN y *E. coli* en superficie peritoneal (B)**

La preparación del inóculo se realiza en agua destilada con una suspensión de *E. coli* ATCC 25922 a diferentes concentraciones de unidades formadoras de colonias por mililitro (UFC/ml). En un inicio se compara la concentración del inóculo en un espectrofotómetro y verifica con un espectrómetro de DADE.

Partiendo de esta suspensión se preparan tantos tubos como ratas se van a inocular, añadiendo a 1ml de la suspensión la cantidad de ml de agua destilada a ensayar. Se comprueba que la concentración bacteriana se ajusta a lo esperado realizando diluciones seriadas. Para ello se siembran en recuento en un agar sangre. Tras extensión se realiza control y lectura a las 18-24 h a 37ºC.

El tiempo transcurrido entre la preparación del inóculo y la inoculación siempre es inferior a 2 horas en todos los casos ensayados

Estudio terapéutico. Una vez encontrada la dosis letal, se realiza aleatorización en tres grupos de animales: grupo I (con suero fisiológico), grupo II (con ceftriaxona), grupo III (con ceftriaxona más alicina). Inclusión de 6 ratas en grupo control (conocimiento de la dosis letal y aplicación del principio de las tres Rs.) y 9 ratas en los grupos II y III. Para el cálculo de tamaño muestral se tienen en cuenta estudios de modelos anteriores [4, 7 ,8] y las normas en las que se basan los principios éticos para minimizar el uso de animales en la investigación: las tres "Rs": Reducir, Reemplazar y Refinar.

Se genera un modelo de peritonitis en todos los grupos. Las ratas de diferentes grupos nunca son estabulados en el mismo estante.

Durante el ensayo, cuando el animal muere dentro de las primeras 24 horas, se realiza cultivo microbiológico de líquido peritoneal y se toman muestras de hígado, riñón, intestino y peritoneo para evaluación histopatológica (figura 1). Con el resto de animales se espera al día del sacrificio o séptimo día de tratamiento. Los parámetros valorados son: congestión hepática, polimorfonuclerares (PMN) en sinusoides hepáticos, PMN en superficie de hígado y peritoneo y colonización de bacterias en superficie de hígado y peritoneo (figura 2).

RESULTADOS

Estudio piloto. Se utilizan 9 ratas para realizar el estudio piloto (tres por cada una de las concentraciones indicadas). Con dichas concentraciones y dilución se observa que todas

Tabla 1 **Resumen de los diferentes estudios realizados. Se muestra el empleo del inóculo de *E. coli* a diferentes concentraciones y las diluciones administradas a nivel intraperitoneal. También se muestran los resultados de cultivos de líquido peritoneal con su respectivo antibiograma.**

	Inóculo *E. coli*[a] 1cc/UFC	Dilución agua destilada (cc)	Ratas (n)	Éxitus	Grupo tratamiento[b]	Cultivo líquido peritoneal	Sensibilidad[c]
ENSAYO PILOTO	10^8 UFC	-	3	0		*E. coli*	Multisensible
	10^9 UFC	-	3	0		*E. coli*	Multisensible
	10^{10} UFC	-	3	0		*E. coli*	Multisensible
	10^{10} UFC	10 cc	3	1		*E. coli*	Multisensible
	10^{10} UFC	15 cc	3	3		-	-
ENSAYO TERAPÉUTICO	10^{10} UFC	15 cc	6	6	Grupo I	*E. coli*	Multisensible
	10^{10} UFC	15 cc	9	1	Grupo II	*E. coli*	Multisensible
	10^{10} UFC	15 cc	9	0	Grupo III	-	-

[a] ***E.coli* ATCC 25922 con sensibilidad a ampicilina, vancomicina y teicoplanina.**

[b] **Grupos de tratamiento : Grupo I - control, Grupo II- antibiótico, Grupo III- antibiótico más adyuvante**

[c] **Sensibilidad de antibiograma Multisensible: ampicilina, vancomicina y teicoplanina.**

UFC: Unidad formadora de colonias.

las ratas sobreviven tras la inyección intraperitoneal a pesar de la ausencia de tratamiento antibiótico. A continuación se estudia la posibilidad de aumentar el volumen de dilución a 10 ml utilizando la concentración más alta de 10^{10} UFC/ml. De las tres analizadas sólo una de ellas muere antes de las 24 horas. Finalmente se establece que el volumen óptimo para producir el 100% de las muertes en las primeras 6 horas del animal es de 15 ml (las tres ratas mueren tras la inyección intraperitoneal de dicha dilución) (tabla 1).

Ensayo terapéutico. Posteriormente determinada la concentración y la dilución óptima para provocar una peritonitis eficaz en el estudio piloto se realiza el ensayo terapéutico con la dilución de 15 ml de agua destilada en el grupo I (control), todas las ratas fallecen entre las 4 y 6 horas siguientes. En todas ellas se toman muestras de líquido peritoneal y sangre verificando que se encuentra una cepa de *E. coli* con idéntica sensibilidad antibiótica a la utilizada para la inoculación.

En el grupo II y III a la vez que se produce la inoculación, son tratadas con antibiótico. Se observa que sobreviven todas (18 ratas) excepto una, en la cual se verifica cepa de *E. coli* en el análisis de líquido peritoneal con similar sensibilidad en antibiograma.

Cuando el animal fallece dentro de las primeras 24 horas se realiza cultivo de líquido peritoneal. En todos los casos se observa el crecimiento de *E. coli* con idéntica sensibilidad antibiótica a la utilizada en la inoculación (tabla 1).

En la valoración histiopatológica se observa formación de abscesos en la superficie del hígado, gran infiltración de polimorfonucleares (PMN) y colonias bacterianas (figura 2).

También se pueden observar PMN y abundantes colonias de *E. coli* en la superficie peritoneal.

DISCUSIÓN

Algunos autores recalcan la importancia de conseguir un modelo estandarizado en el que el proceso séptico se induzca de una forma fácil y reproducible. Estos mismos autores crean un modelo de peritonitis a partir de material fecal de origen humano. Las heces se recogen y procesan de manera protocolaria y son inyectadas intraperitonealmente en los animales [9]. Otro de los modelos probados es la colocación de "stent" en la pared del colon ascendente (colon ascendens stent peritonitis – CASP). Este resuelve uno de los problemas que pueden ocurrir con CLP, que es la formación de un absceso intraabdominal en lugar de un shock séptico por peritonitis. El CASP es un modelo relativamente nuevo y poco común de peritonitis difusa polimicrobiana que reproduce la clínica de una peritonitis aguda [10], además de alterar el flujo sanguíneo cecal con necrosis secundaria de la pared intestinal. La principal desventaja de CASP en comparación con CLP es su mayor complejidad.

El modelo desarrollado en este estudio parte de la referencia en la literatura de generar peritonitis mono microbiana con *E. coli*. Sanchez et al [11] describen dosis letales en ratas sanas, con cirrosis con y sin ascitis, aplicando inóculos de *E. coli* a diferentes concentraciones y diluciones en ratas sanas entre 180-230 gramos. Observan que la mortalidad a corto plazo en menos de 48 horas con un inóculo de 1 ml de *E. coli con* 10^8 y 10^9 UFC diluido en 20 ml de agua estéril (78% y 100% de *E. coli* respectivamente) aumentaba significativamente la mortalidad. Sin embargo observan que estas mismas dosis en ratas sanas con pesos de 450-500 gramos no presentan mortalidad. Esto les lleva a concluir que la mortalidad puede estar relacionada directamente con el volumen inyectado en cavidad peritoneal [12]. Estos mismos autores describen como las ratas con cirrosis sin ascitis muestran que la mortalidad a corto plazo dependía de la concentración de *E. coli* administrada, independiente-

mente del volumen administrado. Cuando las concentraciones son bajas de *E. coli* (10^7 UFC/ml), solo una rata fallece (1/13). Sin embargo cuando se inocula 10^8 UFC/ml de *E. coli* se observa que la mortalidad aumenta, pero significativamente menor a la producida con 10^9 UFC/ml (63% -23/37- vs 95% -35/37-); p<0,01) [13]. Este modelo concuerda con lo encontrado por otros autores [12] y es similar a lo descrito en el modelo que presentamos.

En nuestro modelo se inocula inicialmente con 1 ml de *E. coli* con 10^8, 10^9 y 10^{10} UFC, basándonos en que la concentraciones altas independientes del volumen eran suficientes para producir una sepsis sin mortalidad alguna. En segunda instancia se inocula una concentración de 10^{10} UFC, añadiendo un volumen de dilución de 10 y 15 ml de agua estéril para corroborar que tanto la concentración como el volumen son determinantes en el desarrollo de sepsis. Sin embargo, con estas premisas encontramos una mortalidad del 33% en las que recibieron 10 ml, mientras quienes reciben 15 ml fallecen 100% en menos de 6 horas. Esto coincide con lo descrito en la literatura, aunque en nuestro caso el volumen administrado es ligeramente inferior al utilizado en otros trabajos [11].

Finalmente al realizar el ensayo terapéutico se confirma que el 100% de las ratas control fallecen dentro de las primeras 6 horas por inoculación de *E. coli* al 10^{10} UFC diluidas en 15 ml.

Este modelo experimental mono bacteriano presenta ciertas ventajas y desventajas. Por una parte al conocer el germen, la cepa y la cantidad del inóculo que administramos, puede ser muy útil en el estudio de cambios fisiopatológicos de la sepsis, ya que somos capaces de controlar las condiciones bajo las que se produce. Algunos autores [13] afirman que este modelo en roedores es capaz de reproducir varios cambios característicos de la sepsis humana, pero su relevancia clínica está limitada por el hecho de que son necesarias elevadas concentraciones de bacterias en un modelo con un huésped incapaz de localizar la infección, a diferencia de lo que viene ocurriendo en humanos [14]. Además la mayoría de modelos infectan a ratas sanas, jóvenes y sin comorbilidades a diferencia de los humanos donde las poblaciones más vulnerables son los extremos de la vida con comorbilidades y donde el tratamiento de la sepsis es multidisciplinario incluyendo estrategias de nutrición, soporte ventilatorio, soporte hemodinámico, etc. Hasta el momento se han descrito muchos modelos de sepsis en experimentación animal, pero ninguno logra reproducir completamente la sepsis en humanos ya que se trata de un proceso heterogéneo, dependiente de la susceptibilidad genética de cada individuo y se acompaña de importantes comorbilidades y consumo de fármacos [13].

Las líneas de investigación se centran actualmente en el uso de ratones "humanizados". Se trata de ratones que son trasplantados con células madre hematopoyéticas humanas que llevan a cabo la respuesta inflamatoria [15, 16]. El principal inconveniente es que para obtener estos ratones el procedimiento es lento y de coste elevado. Otra forma de mejorar los modelos sería obtener ratones de más edad con/sin comorbilidades asociadas.

El modelo aquí descrito establece una dosis letal de *E. coli* de 10^{10} UFC diluida en 15 ml agua estéril. Tras una inyección intraperitoneal genera una infección eficaz, controlada y fácilmente reproducible que podría servir de base para la realización de futuras líneas de investigación.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Gina Osorio
Leticia Fresco
Ester Monclús
Míriam Carbó
Mar Ortega

Adecuación del uso de antibióticos de "Categoría Especial" en el Servicio de Urgencias de un hospital de tercer nivel

Área de Urgencias, Hospital Clínic de Barcelona.

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RESUMEN

Objetivo. Analizar la adecuación de las prescripciones de antibióticos de categoría especial (ATB de CE) en el Servicio de Urgencias Hospitalario (SUH) de un centro urbano de tercer nivel.

Material y métodos. Se seleccionó una muestra aleatoria de 100 pacientes diferentes a los que se les inició un ATB de CE en Urgencias durante el año 2018. El equipo investigador revisó la historia clínica del episodio de urgencias y de ingreso. Se determinó mediante regresión logística los factores independientes asociados con el grado de adecuación del tratamiento.

Resultados. Se analizaron 97 prescripciones de las cuales 66 (68%) cumplían los criterios de prescripción adecuada. El grado de adecuación fue del 70% si la infección estaba relacionada con la asistencia sanitaria y del 75% si el paciente tenía factores de riesgo de infección por microorganismos multirresistentes (MMR). El porcentaje de adecuación fue mayor en los casos en los que se especificó el foco de la infección (72%) y la gravedad del episodio (73%). Las variables independientes que se asociaron a una prescripción adecuada fueron: la presencia de factores de riesgo de infección por MMR (OR: 2,35 IC 95%: 1,65 – 3,17 p: 0,01), el especificar el foco de la infección (OR: 3,79 IC 95%: 1,72 – 4,22 p: 0,02) y señalar la gravedad del episodio (OR: 3,09 IC 95%: 1,12 – 3,09 p: 0,03).

Conclusiones. La prescripción de los ATB de CE en el SUH es adecuada en la medida que se tenga en cuenta el ámbito de adquisición de la infección, los factores de riesgo de MMR, el foco de infección y la gravedad del cuadro clínico.

Palabras clave: Adecuación tratamiento antibiótico, antibióticos de categoría especial, programas de optimización de uso de antimicrobianos

Correspondencia:
Dra. Mar Ortega Romero
Área de Urgencias, Hospital Clínic de Barcelona
C/ Villarroel 170, 08036 Barcelona
España
Tfno.: +3493227983 - Fax: +34932275693
E-mail: mortega@clinic.cat

Adequacy of the special category antibiotics prescriptions in the Emergency Department of a third level urban Hospital

ABSTRACT

Objective. The aim of the study was to analyze the adequacy of the special category antibiotics prescriptions in the Emergency Department (ED) of a third level urban Hospital.

Material and methods. A random sample of 100 different patients who were started with a special category antibiotic along 2018 in the ED was selected. The research team reviewed the medical history of the emergency and admission episode. The independent factors associated with the degree of adequacy of the treatment were determined by logistic regression.

Results. A total of 97 prescriptions were analyzed of which 66 (68%) met the criteria of adequate prescription, 23 (24%) adequate prescription, but with equally recommended alternatives and 8 (8%) were inappropriate prescriptions. The degree of adequacy was 70% if the infection was related to healthcare and 75% if the patient had risk factors for multiresistant (MR) microorganisms' infection. The percentage of adequacy was higher in the cases in which the focus of the infection (72%) and the severity of the episode (73%) were specified. The independent variables that were associated with an adequate prescription were: the presence of risk factors for MR microorganisms' infection (OR: 2.35 95% CI: 1.65 - 3.17 p: 0.01), if the focus of the infection (OR: 3.79 95% CI: 1.72 - 4.22 p: 0.02) and the severity of the episode (OR: 3.09 95% CI: 1.12 - 3.09 p: 0.03) were specified.

Conclusions. The prescription of special category antibiotics in ED is appropriate if the clinical guidelines are followed and if the setting of infection acquisition, the risk factors of MR microorganisms, the focus and the severity of infection are taken into account in clinical picture.

Key words: Adecuacy of antibiotic treatment, special category antibiotics, antimicrobial use optimization programs

INTRODUCCIÓN

Las enfermedades infecciosas son uno de los principales motivos de consulta en los servicios de urgencias y los antibióticos uno de los grupos farmacológicos prescritos con mayor frecuencia [1]. Según la Organización Mundial de la Salud (OMS), la no adherencia a las guías de práctica clínica y la prescripción indiscriminada de antibióticos de espectro mayor al necesitado son dos de las primeras causas de aparición de resistencias antimicrobianas, ya consideradas como un problema de salud pública a nivel mundial [2, 3]. Además, el uso inadecuado de antimicrobianos se relaciona con una mayor incidencia de fracaso terapéutico, un aumento de la morbimortalidad y una utilización ineficiente de los recursos [4-6]. La Sociedad Americana de Enfermedades Infecciosas (IDSA) recomienda la implementación de guías de tratamiento empírico adaptadas a la ecología local de cada centro para evitar la aparición de resistencias y como herramienta para disminuir la morbimortalidad, la estancia hospitalaria y los costes sanitarios [7]. En los últimos años se han desarrollado, además, programas de optimización de uso de antimicrobianos (PROA) centrados fundamentalmente en el paciente hospitalizado [8-10]. El servicio de urgencias hospitalario (SUH) supone, en la mayoría de los casos, la puerta de entrada al sistema sanitario estimándose la tasa de prescripciones antibióticas en éste área la más elevada dentro de la atención sanitaria [11]. Se trata, por lo tanto, de un lugar clave para el desarrollo de este tipo de programas al tener un impacto no sólo en el paciente ambulatorio, sino también en el paciente hospitalizado.

En este contexto de aumento de la incidencia de las infecciones relacionadas con la asistencia sanitaria y de los microrganismos con mecanismos de resistencia se han introducido en práctica médica nuevos antimicrobianos que se han denominado de 'categoría especial' (ATB de CE). Son antibióticos que, por su espectro, características farmacocinéticas y farmacodinámicas, así como por su coste están sometidos a un seguimiento por los equipos de optimización de antibióticos de los centros hospitalarios.

Por todo lo expuesto anteriormente y dado que los SUH son cruciales en el diagnóstico y tratamiento de las enfermedades infecciosas, nos planteamos el presente estudio con el objetivo de analizar la adecuación de las prescripciones de los ATB de CE en el área de urgencias de un hospital urbano de tercer nivel.

MATERIAL Y MÉTODOS

Tipo y ámbito del estudio. Estudio de cohortes retrospectivo realizado en un hospital urbano y universitario de tercer nivel que cuenta con un SUH que atiende aproximadamente 95.000 consultas anuales. El hospital asume la asistencia sanitaria especializada de una población estimada de 500.000 personas. La asistencia del SUH está organizada por niveles de gravedad según el modelo de triaje establecido. El SUH consta de un área de primera asistencia donde se atiende a los pacientes estables y un área de críticos y otra de semi-críticos, donde se atiende a los pacientes más graves. También consta de un área de observación de 28 camas donde se derivan los pacientes ya visitados en espera del alta o de cama de hospitalización para ingreso.

Criterios de inclusión. Se seleccionaron aquellos pacientes adultos (mayores de 18 años) que durante el año 2018 fueron atendidos en nuestro SUH y se les prescribió un ATB de CE. Los ATB de CE que se incluyeron fueron: ceftarolina, ceftazidima-avibactam, ceftolozano-tazobactam, dalbavancina, daptomicina, fidaxomicina, linezolid, tedizolid, telavancina y tigeciclina. Para identificar estos enfermos se revisaron los archivos de prescripción de Farmacia Hospitalaria y se seleccionó una muestra aleatoria de 100 pacientes manteniendo el porcentaje del antibiótico prescrito. Se realizó un listado codificado de los pacientes incluidos y se revisó la historia clínica del episodio que requirió el inicio de dicho antibiótico incluyendo el episodio de urgencias y el episodio de ingreso hasta el momento del alta.

Variables independientes. Se recogieron las siguientes características clínico-epidemiológicas del paciente de acuerdo con una hoja de recogida de datos diseñada a tal efecto: edad, sexo, comorbilidades principales, factores predisponentes a la infección y factores de riesgo de infección por microorganismos multirresistentes (MMR). Los factores de riesgo de infección por MMR que se registraron fueron los siguientes: ingreso previo en los últimos tres meses, tratamiento antibiótico previo en los últimos tres meses y aislamientos previos de MMR en los últimos seis meses.

Respecto al episodio revisado se recogió el tipo de ATB de CE pautado y el ámbito de adquisición de la infección definida como: nosocomial (si el último ingreso previo se produjo en un período inferior a tres semanas con respecto al episodio de urgencias), en relación con la asistencia sanitaria (ingreso en hospital de agudos en los 3 meses previos y que no se incluye en la categoría de nosocomial, paciente en hemodiálisis o quimioterapia activa, paciente ingresado en centro sociosanitario) o comunitaria si no se podía incluir en cualquiera de las otras categorías. También se recogió el médico prescriptor, el motivo de la prescripción, si el foco probable de la infección fue especificado por el prescriptor y cuál fue, la gravedad del episodio (en base a los criterios Sepsis-3) [12] y si esta se especificó en la historia clínica, la presencia o no de insuficiencia renal aguda o crónica (según los criterios de la 'Kidney Disease Improving Global Outcomes') [13] así como de neutropenia (recuento de neutrófilos menor de 1 x 10^9/L). También se registró si se realizó toma de muestra para pruebas microbiológicas antes del inicio del antibiótico y el resultado de estas, si la terapia fue con un solo antibiótico o combinada, la unidad de ingreso del paciente y el estado final del mismo (vivo o muerto) al finalizar el episodio.

Variable dependiente. Se consideró como variable dependiente o resultado del estudio el grado de adecuación del tratamiento antibiótico en el episodio analizado en base a la guía clínica de terapéutica antimicrobiana usada en nuestro centro [14]. El grado de adecuación del tratamiento antibiótico se dividió en tres categorías:

• Categoría 1: Prescripción adecuada en cuanto a espectro, gravedad, dosis, ajuste a función renal, intervalo entre dosis y vía de administración. Se valoró que el ATB de CE fue prescrito de forma adecuada cuando se realizó de acorde a la guía antimicrobiana usada de forma general en el centro considerando los siguientes aspectos: el riesgo de infección por MMR, la gravedad del episodio, así como el ajuste de la dosis a la función renal.

• Categoría 2: Prescripción adecuada, pero existen alternativas igualmente recomendadas. Cuando la prescripción fue adecuada (cumplía todas las características de la categoría anterior), pero existían alternativas igualmente válidas según la guía clínica.

• Categoría 3: Prescripción inadecuada. Cuando la prescripción no cumplía todas las condiciones para incluirla en una de las categorías previas.

Las prescripciones, historia clínica y pruebas complementarias de cada uno de los pacientes incluidos fueron revisadas por el equipo investigador y se contó con la ayuda de un consultor en Enfermedades Infecciosas y otro en Farmacia Hospitalaria para consensuar la valoración en los casos dudosos.

Análisis estadístico. El análisis de resultados se realizó con el programa estadístico SPSS (versión 20.0; SPSS, Inc., Chicago, EE. UU.). Las variables continuas se presentaron en forma de media y desviación estándar (DE) o mediana (según su homogeneidad) y las variables categóricas en forma de porcentajes. Para hacer el análisis comparativo se utilizó la prueba de Ji cuadrado para comparar variables categóricas y la T de Student para las variables continuas. Se determinó mediante regresión logística los factores independientes asociados con el grado de adecuación del tratamiento con ATB de CE. Para ello se recodificó la variable dependiente en dos categorías: prescripción adecuada (categoría 1) vs segunda y tercera categorías juntas.

Comité de ética de investigación. El estudio fue aceptado por el Comité Ético de Investigación (CEI) del Hospital Clínic de Barcelona (número de referencia HCB/2018/1114).

RESULTADOS

Durante el año 2018 se iniciaron desde en Urgencias un total de 1.086 tratamientos con alguno de los antibióticos de categoría especial incluidos en el estudio. La distribución porcentual fue la siguiente: linezolid 52%, daptomicina 28 %, ceftarolina 7%, tigeciclina 5%, ceftolozano-tazobactam 4%, ceftazidima-avibactam 3%, otros (tedizolid, dalvabancina, fidaxomicina) menos del 1%.

En la tabla 1 se muestran las características clínicas, epidemiológicas y comorbilidades principales de los 100 pacientes incluidos. Destacamos que un 78% de los pacientes incluidos eran varones y que un 79% presentaban uno o más factor de riesgo de infección por MMR.

Tabla 1 **Características clínico-epidemiológicas de los pacientes incluidos (N=100)**

Edad en años (media, DE)	59 (DE: 16)
Sexo: hombre / mujer	78 / 22
Características clínicas y comorbilidades[a]	
Paciente mayor de 65 años	41
Enfermedad hemato-oncológica en tratamiento activo	34
Diabetes mellitus	20
Cirrosis hepática	15
Portador de prótesis biliar	11
Trasplante de órgano sólido en tratamiento inmunosupresor	10
Portador de prótesis articular	2
Portador de catéter venoso central o prótesis endovascular	8
Paciente ingresado en centro socio sanitario	5
Portador de sonda vesical	5
Insuficiencia renal crónica en hemodiálisis	5
Infección de tracto urinario de repetición	9
Infección VIHb	2
Factores de riesgo de infección por MMR[a,c]	
Ingreso previo en los últimos 3 meses	66
Tratamiento antibiótico previo en los últimos 3 meses	39
Aislamientos previos de MMR[c] (colonización o infección en los últimos 6 meses)	18
Presencia de uno o más factores de riesgo de infección por MMR[c]	
Si	79
No	21

[a]La suma total es superior a 100 porque cada paciente podría tener una o varias comorbilidades o uno o varios factores de riesgo de infección por MMR

[b]VIH: virus de la inmunodeficiencia humana

[c]MMR: microorganismos multirresistentes

Las características del episodio que motivó la prescripción de un antibiótico de categoría especial se muestran en la tabla 2. La mayoría de los tratamientos fueron empíricos (94%) y combinados (87%). En cuanto al ámbito de adquisición de la infección un 57% de las infecciones fueron relacionadas con la asistencia sanitaria y un 24% fueron de adquisición nosocomial. La prescripción del antibiótico de categoría especial fue realizada en un tercio de los casos por el equipo médico de urgencias, un tercio por el equipo médico de enfermedades infecciosas y un tercio por el equipo médico de otra especialidad. En la mayoría de los casos tanto el posible foco de la infección (89%) como la gravedad del cuadro clínico (86%) fueron especificadas en la historia clínica. El foco de infección más frecuente fue el de piel y partes blandas seguido por el foco respiratorio. Un 60% de pacientes presentaban criterios de sepsis y un 14% de shock séptico. El 73% de los pacientes ingresó en hospitalización convencional y el 18% en unidad de cuidados intensivos o semi-intensivos. La mortalidad de la serie fue de un 10%.

En cuanto a la adecuación de las prescripciones de los 100 casos incluidos se pudieron analizar 97 (finalmente se excluyeron tres pacientes ya que sólo recibieron una única dosis de ATB de CE). De estas 66 (68%) cumplían los criterios de

Tabla 2 Características del episodio que motivó la prescripción de un antibiótico de categoría especial (N=100)

ATB de CE pautado	
Linezolid	50
Daptomicina	29
Ceftarolina	7
Ceftazidima-avibactam	3
Fidaxomicina	3
Tigeciclina	4
Ceftolozano-tazobactam	4
Adquisición infección	
Relacionada con cuidados sanitarios	57
Nosocomial	24
Comunitaria	19
Médico prescriptor	
Equipo médico de otra especialidad	36
Equipo médico de enfermedades infecciosas	33
Equipo médico de urgencias	31
Motivo de la prescripción	
Empírico	94
Profilaxis	3
Dirigido	3
Foco de la infección especificado por el prescriptor	
Si	89
No	11
Foco de la infección	
Piel y partes blandas	27
Respiratorio	21
Desconocido	11
Prótesis biliar	10
Abdominal	9
Osteoarticular	8
Endovascular o dispositivos endovasculares	2
Sistema nervioso central	2
Gravedad indicada por el prescriptor	
Si	86
No	14
Gravedad del episodio	
Sepsis	60
Shock séptico	14
Situaciones especiales	
Insuficiencia renal crónica	20
Insuficiencia renal aguda	13
Neutropenia	2
Toma de muestra antes del antibiótico	
Si	97
No	3
Tipo de prescripción	
Combinado	87
Monoterapia	13
Resultado de pruebas microbiológicas	
Negativo	64
Positivo monomicrobiano	32
Positivo polimicrobiano	4
Destino del paciente desde Urgencias	
Ingreso en sala convencional	73
Ingreso en UCI-intermedios	18
Hospitalización a domicilio	5
Traslado a otro centro	4
Estado del paciente al final del episodio	
Vivo	87
Muerto	10
Desconocido	3

prescripción adecuada, 23 (24%) prescripción adecuada, pero con alternativas igualmente recomendables y 8 (8%) fueron clasificadas como prescripciones inadecuadas. En la tabla 3 se muestran los factores asociados con el grado de adecuación de las prescripciones de ATB de CE. Las prescripciones con mayor porcentaje de adecuación fueron daptomicina (77%), linezolid (68%) y ceftolozano-tazobactam (100%). El grado de adecuación fue del 70% si la infección estaba relacionada con la asistencia sanitaria y del 75% si el paciente tenía factores de riesgo de infección por MMR. Asimismo, el grado de adecuación fue mayor en los casos en los que se especificó el foco de la infección (72%) y la gravedad del episodio (73%). En los casos de shock séptico el grado de adecuación fue del 93%.

Finalmente se analizó mediante estudio multivariado los factores independientes asociados con la adecuación de la prescripción comparando esta con la segunda y tercera categorías juntas (tabla 4). Las variables que se asociaron a una prescripción adecuada de ATB de CE fueron: la presencia de factores de riesgo de infección por MMR (OR: 2,35 IC 95%: 1,65 – 3,17 p: 0,01), el especificar el foco de la infección (OR: 3,79 IC 95%: 1,72 – 4,22 p: 0,02) y señalar la gravedad del episodio (OR: 3,09 IC 95%: 1,12 – 3,09 p: 0,03).

DISCUSIÓN

España es uno de los países europeos con mayor número de prescripciones antibióticas ambulatorias [15]. La mayoría de los estudios acerca de la adecuación del tratamiento antibiótico se han realizado en el paciente hospitalizado. Según estos estudios previos, se considera que entre el 20% y el 50% de las prescripciones antibióticas en el paciente hospitalizado son inapropiadas o innecesarias [16]. Otros trabajos realizados en esta área demuestran, además, que la no adherencia a guías de práctica clínica, el uso de antimicrobianos con un espectro más amplio del necesitado y la duración excesiva de tratamientos son frecuentes [6, 7].

Las infecciones son uno de los motivos de consulta más

Tabla 3 **Características y factores relacionados con la adecuación del tratamiento antibiótico de categoría especial (% calculado sobre el total de la fila).**

Variable		Prescripción adecuada N= 66 (68%)	Prescripción adecuada, pero con alternativas N= 23 (24%)	Prescripción inadecuada N=8 (8%)	Total= 97
ATB de CE pautado	Linezolid	34 (68%)	16 (32%)	0 (-)	50
	Daptomicina	20 (77%)	2 (8%)	4 (15%)	26
	Ceftarolina	2 (29%)	5 (71%)	0 (-)	7
	Ceftazidima-avibactam	1 (33%)	0 (-)	2 (66%)	3
	Fidaxomicina	1 (33%)	2 (66)	0 (-)	3
	Tigeciclina	2 (50%)	0 (-)	2 (50%)	4
	Ceftolozano-tazobactam	4 (100%)	0 (-)	0 (-)	4
Adquisición de la infección	Comunitaria	9 (47%)	10 (53%)	0 (-)	19
	Relacionada asistencia sanitaria	40 (70%)	11 (19%)	6 (11%)	57
	Nosocomial	17 (81%)	2 (9%)	2 (9%)	21
Factor de riesgo de MMR	No	9 (43%)	12 (57%)	0 (-)	21
	Sí	57 (75%)	11 (14%)	8 (11%)	76
Médico prescriptor	Equipo médico de urgencias	25 (81%)	5 (16%)	1 (3%)	31
	Equipo médico de infecciones	17 (57%)	10 (33%)	3 (10%)	30
	Equipo médico de otra especialidad	24 (67%)	8 (22%)	4 (11%)	36
Insuficiencia renal	No	43 (67%)	15 (23%)	6 (9%)	64
	Aguda	11 (85%)	2 (15%)	0 (-)	13
	Crónica	12 (60%)	6 (30%)	2 (10%)	20
Foco de la infección	No especificado	2 (25%)	0 (-)	6 (75%)	8
	Sí especificado	64 (72%)	23 (26%)	2 (2%)	89
Gravedad de la infección señalada por el prescriptor	No especficado	3 (27%)	4 (36%)	4 (36%)	11
	Sí especificado	63 (73%)	19 (22%)	4 (5%)	86
Gravedad de la infección	No sepsis	14 (61%)	5 (22%)	4 (17%)	23
	Sepsis	39 (65%)	17 (28%)	4 (7%)	60
	Shock séptico	13 (93%)	1 (7%)	0 (-)	14
Mortalidad	Muerto	9 (90%)	1 (10%)	0 (-)	10
	Vivo	57 (66%)	22 (25%)	8 (9%)	87

MMR: microorganismos multirresistentes

frecuente en Urgencias [1]. La mayoría de los tratamientos antibióticos tanto ambulatorios como de los pacientes ingresados se inician en urgencias. En el ámbito de los SUH el trabajo de Yunquera et al aporta unos datos interesantes [11]. De acuerdo con sus resultados, el 43,2% de las prescripciones antibióticas no estaban indicadas; cuando lo estaban, el 38% de los antibióticos no eran correctos según las guías locales y la pauta y duración elegidas no fueron correctas en el 17,2% y 54,6% de los casos. Los autores concluyen que sería interesante implantar un programa de optimización del tratamiento antibiótico ya que esto podría suponer la mejora de la prescripción antibiótica, con la consiguiente reducción del impacto ecológico, permitiendo así una utilización de los recursos más eficiente y una mejora de la calidad asistencial. Esto está en línea con

Tabla 4 **Análisis multivariado de los factores relacionados con la adecuación del tratamiento antibiótico de categoría especial (% calculado sobre el total de la fila).**

Variable	Prescripción categoría 1[a] N= 66	Prescripción categoría 2-3[b] N= 31	Total 97	P[c]	OR	IC 95%	P[d]
Adquisición de la infección							
Comunitaria	9 (47%)	10 (53%)	19	0,07	1		
Relacionada asistencia sanitaria	40 (70%)	17 (13%)	57		0,81	0,18-2,01	0,22
Nosocomial	17 (81%)	4 (19%)	21		0,85	0,75-2,56	0,54
Factor de riesgo de MMR							
No	9 (43%)	12 (57%)	21	0,008	1		
Si	57 (75%)	19 (25%)	76		2,35	1,65-3,17	0,01
Médico prescriptor							
Equipo médico de urgencias	25 (81%)	6 (19%)	31	0,1	1		
Equipo médico de infecciones	17 (57%)	13 (43%)	30		0,55	0,09-3,24	0,51
Equipo médico de otra especialidad	24 (67%)	12 (33%)	36		0,47	0,10-2,03	0,30
Insuficiencia renal							
No	43 (67%)	21 (33%)	64	0,3	1		
Aguda	11 (85%)	2 (15%)	13		3,07	0,85-9,51	0,8
Crónica	12 (60%)	8 (40%)	20		2,45	0,29-2,38	0,41
Foco de la infección							
No especificado	2 (25%)	6 (75%)	8	0,01	1		
Si especificado	64 (72%)	25 (28%)	89		3,79	1,72-4,22	0,02
Gravedad de la infección señalada por el prescriptor							
No especificado	3 (27%)	8 (73%)	11	0,004	1		
Si especificado	63 (73%)	23 (27%)	86		3,09	1,12-3,27	0,03
Gravedad de la infección							
No sepsis	14 (61%)	9 (39%)	23	0,06	1		
Sepsis	39 (65%)	21 (35%)	60		1,57	0,75-3,64	0,07
Shock séptico	13 (93%)	1 (7%)	14		2,65	0,91-7,65	0,05

[a]**Prescripción adecuada categoría 1**

[b]**Adecuación categoría 2 (adecuado pero otras recomendaciones igualmente válidas) y categoría 3 (inadecuado)**

[c]**Análisis univariado**

[d]**Análisis multivariado**

lo que proponen Oltra et al en su estudio realizado en el área de observación de urgencias de su centro y en el que concluyen que el tratamiento antimicrobiano adecuado fue inferior al 50% [17].

En el contexto actual de aumento de la incidencia de las infecciones relacionadas con la asistencia sanitaria y de los microorganismos con mecanismos de resistencia los SUH son cruciales a la hora de iniciar el tratamiento antibiótico y las prescripciones de ATB de CE han aumentado en los últimos años. En general, los programas de optimización del tratamiento antibiótico se centran en el paciente hospitalizado y en la duración y ajuste del tratamiento a los aislamientos. Sin embargo, no hemos encontrado trabajos que investiguen de forma concreta la adecuación en la prescripción inicial de los ATB de CE en los SUH, ya que los estudios previos comentados investigan los antibióticos prescritos con más frecuencia como betalactámicos y fluoroquinolonas.

De acuerdo con nuestros resultados observamos, en primer lugar, que la prescripción de ATB de CE es frecuente en nuestro SUH. Durante el año 2018 se iniciaron un total de 1.086 tratamientos con alguno de los ATB de CE incluidos en el estudio. Esto se puede explicar porque nuestro centro proporciona asistencia especializada en enfermedades complejas por lo que recibe pacientes referidos de otras áreas asisten-

ciales. Además, el porcentaje de aislamientos en hemocultivos de microorganismos gramnegativos con mecanismos de resistencias fue del 30% en el ámbito intrahospitalario en el mismo período.

En segundo lugar, el tratamiento empírico iniciado en urgencias con ATB de CE es adecuado en un alto porcentaje de casos (68%). Es destacable que el 24% de las prescripciones fueron adecuadas, pero con alternativas igualmente recomendables. Esto puede ser debido a que la guía clínica más usada en nuestro centro aconseja diferentes opciones dentro de la misma entidad nosológica. Es posible que el médico prescriptor se decante por un ATB de CE frente a las otras recomendaciones por la percepción probablemente subjetiva de que pueda ser más eficaz para su paciente.

En tercer lugar, las prescripciones fueron inadecuadas en 8 pacientes (8%). Estas prescripciones fueron inadecuadas en todos los casos porque se usó un ATB de CE para cubrir un espectro antimicrobiano diferente del que se esperaba por el tipo de infección, el estado clínico del paciente y los factores de riesgo de MMR presentes. Además, en tres casos la dosis no se ajustó a la función renal. Por otro lado, no existieron diferencias entre el porcentaje de adecuación de los tratamientos prescritos por el equipo médico de Urgencias con respecto a los otros equipos médicos de guardia. Es cierto que de las prescripciones realizadas por el equipo médico de urgencias sólo un 3% (1 paciente) fue inadecuada, respecto a un 10% (3 pacientes) de las realizadas por el equipo médico de infecciones y un 11% (4 pacientes) de las realizadas por el equipo médico de otra especialidad. Estas diferencias no fueron estadísticamente significativas y es posible que estén condicionadas por el pequeño tamaño de la muestra. Además, podrían explicarse en base a que durante la revisión de las historias clínicas tuvimos la impresión de que los casos más complejos se comentaban con infectología, cirugía general y otras especialidades. Por lo que es posible que la prescripción inadecuada fuera debido a la complejidad del cuadro clínico. En cualquier caso, lo más interesante es que si el equipo médico sigue las recomendaciones de la guía de práctica clínica y realiza una buena historia clínica considerando el ámbito de adquisición de la infección, los factores de riesgo de MMR, así como el foco de infección y la gravedad del episodio, el grado de adecuación es superior al 70%.

Nuestro estudio presenta una serie de limitaciones. La primera es que al tratarse de una cohorte retrospectiva no se pudo entrevistar al médico prescriptor para conocer los motivos por los que decidió una pauta antibiótica respecto a otra. Además, el tamaño de la muestra es pequeño y puede condicionar sesgos que condicionen la validez interna. Por otro lado, las características de nuestro centro (hospital urbano de tercer nivel y con patología referida) en el que hay equipo de guardia prácticamente de todas las especialidades condiciona que los resultados no puedan ser extrapolados totalmente a otros centros hospitalarios de menor complejidad. Por último, el diseño del estudio no permitió analizar la duración del tratamiento antibiótico ni tampoco si se ajustó al aislamiento microbiológico durante el ingreso.

En conclusión, los SUH son un área asistencial clave en la patología infecciosa y en consecuencia en el inicio del tratamiento antibiótico. En los últimos años hemos asistido a un aumento en la incidencia de infecciones relacionadas con la asistencia sanitaria y por microorganismos con factores de resistencia. Por este motivo, se ha constatado un aumento en las prescripciones desde Urgencias de los ATB de CE. Los equipos de urgencias están preparados para hacer una prescripción adecuada de estos antibióticos si se realiza una buena historia clínica considerando los factores de riesgo de MMR, el foco de infección y la gravedad del cuadro clínico y haciendo un buen uso de las guías de práctica clínica.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Sadaf Zafar Iqbal-Mirza[1]
Raquel Estévez-González[1]
Vicente Serrano-Romero de Ávila[1]
Elena de Rafael González[2]
Eva Heredero-Gálvez[3]
Agustín Julián-Jiménez[1,4]

Factores predictores de bacteriemia en los pacientes atendidos en el Servicio de Urgencias por infección

[1]Servicio de Urgencias - Área de Medicina Interna, Complejo Hospitalario Universitario de Toledo. Toledo, España.
[2]Servicio de Análisis Clínicos y Bioquímica, Complejo Hospitalario Universitario de Toledo. Toledo, España.
[3]Servicio de Microbiología y Parasitología, Complejo Hospitalario Universitario de Toledo. Toledo, España.
[4]Universidad de Castilla La Mancha, España.

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RESUMEN

Objetivos. Analizar los factores predictivos de bacteriemia en los pacientes atendidos en el servicio de urgencias (SU) por un episodio de infección.

Pacientes y métodos. Estudio observacional, retrospectivo, descriptivo y analítico de todos los hemocultivos extraídos en un SU en los pacientes adultos (≥ 18 años) atendidos por infección desde el 1-1-2018 hasta el 1-7-2018. Se realizó seguimiento durante 30 días. Se analizaron 38 variables independientes (epidemiológicas, de comorbilidad, funcionales, clínicas y analíticas) que pudieran predecir la existencia de bacteriemia. Se realizó un estudio univariado y multivariante mediante regresión logística.

Resultados. Se incluyeron 1.425 episodios de hemocultivos extraídos. De ellos se consideraron como bacteriemias verdaderas 179 (12,6 %) y como HC negativos 1.246 (87,4 %). Entre los negativos, 1.130 (79,3%) no tuvieron crecimiento y 116 (8,1%) se consideraron contaminados. Cinco variables se asociaron de forma significativa como predictoras de bacteriemia verdadera: procalcitonina (PCT) sérica ≥ 0,51 ng/ml [odds ratio (OR): 4,52; intervalo de confianza (IC) al 95%: 4,20-4,84; p <0,001], temperatura > 38,3°C [OR: 1,60; IC al 95%: 1,29-1,90; p <0,001], presión arterial sistólica (PAS) < 100 mmHg [OR: 3,68; IC al 95%: 2,78-4,58; p <0,001], shock séptico [OR: 2,96; IC al 95%: 1,78-4,13; p <0,001] y la existencia de neoplasia [OR: 1,73; IC al 95%: 1,27-2,20; p <0,001].

Conclusiones. Existen varios factores disponibles tras una primera valoración en el SU, entre ellos la PCT sérica, la temperatura, la hipotensión con/sin criterios de shock séptico y la existencia de neoplasia, que predicen la existencia de bacteriemia verdadera.

Palabras clave: Servicio de Urgencias, Bacteriemia, Hemocultivos, Biomarcadores, Procalcitonina, Proteína C Reactiva, Factores predictores.

Correspondencia:
Dr. Agustín Julián-Jiménez, MD, PhD.
Servicio de Urgencias-Coordinador de Docencia, Formación, Investigación y Calidad.
Complejo Hospitalario Universitario de Toledo, Toledo, España.
Avda. de Barber nº 30. C.P: 45.004. Toledo
Teléfono: 925269200-ext 48560. FAX: 925269372
E-mail: ajulianjimenez@gmail.com; agustinj@sescam.jccm.es

Predictive factors of bacteraemia in the patients seen in emergency departments due to infections

ABSTRACT

Objectives. The aim of the study was to analyze predictive factors of bacteraemia in patients seen in the emergency department (ED) for an episode of infectious disease.

Patients and methods. Observational, retrospective and descriptive analytical study of all blood cultures extracted in an ED in adult patients (≥ 18 years) seen in ED due to infectious disease from 1-1-2019 to 1-7-2019. The follow-up was carried out during 30 days. Thirty-eight variables for predicting bacteraemia were assessed. They covered epidemiological, comorbidity, functional, clinical and analytical factors. Univariate and multivariate logistic regression analysis was performed.

Results. A total of 1,425 blood cultures were finally enrolled in the study. Of those were considered true bacteremia 179 (12.6 %) and as negative blood cultures 1,246 (87.4 %). Amongst negatives, 1,130 (79.3%) without growth and 116 (8.1%) as contaminants blood cultures. Five variables were significantly associated with true bacteraemia: serum procalcitonin (PCT) ≥ 0.51 ng/ml [odds ratio (OR): 4.52; 95% confidence interval (CI): 4.20-4.84, *P* <.001], temperature > 38.3°C [OR:1.60; 95% CI:1.29-1.90, *P* <.001], systolic blood pressure (SBP) < 100 mmHg [OR:3.68; 95% CI:2.78-4.58, *P* <.001], septic shock [OR:2.96; 95% CI:1.78-4.13, *P* <.001] and malignancy [OR:1.73; 95% CI:1.27-2.20, *P* <.001].

Conclusions. Several factors evaluated in an initial assessment in the ED, including serum PCT, temperature, hypotension (with/without septic shock) and being malignancy, were found to predict true bacteraemia.

Keywords: Emergency Department, Bacteraemia, Blood cultures, Biomarkers, Procalcitonin, C-reactive protein, Predictive factors.

INTRODUCCIÓN

Alrededor del 15% de los pacientes que se atienden en los servicios de urgencias (SU) son diagnosticados de un proceso infeccioso. En su valoración se obtienen muestras para estudios microbiológicos en el 43% de éstos, donde predomina la extracción de hemocultivos (HC) que se lleva a cabo en el 14,6% de los pacientes con infección [1].

Se define como bacteriemia la presencia de bacterias en la sangre que se pone de manifiesto por el aislamiento de éstas en los HC [2]. A pesar de las nuevas técnicas de detección rápida (del ADN del patógeno o por aplicación de espectrometría de masas), los HC permiten el diagnóstico etiológico de la infección, aportan información sobre la sensibilidad del microorganismo aislado y favorecen la optimización del tratamiento antimicrobiano [2-5].

La rentabilidad diagnóstica de los HC obtenidos en los SU es muy variable (2-20%) [3], mientras que los considerados "HC contaminantes", aunque sería deseable que fuesen menos del 3% [2,3], en realidad pueden alcanzar tasas muy superiores [6, 7]. Además, los HC con aislamiento significativo de los pacientes que son dados de alta (la llamada bacteriemia oculta) suponen del 3-5% de los extraídos en el SU [3, 8]. Estos hechos representan verdaderos problemas, al conllevar un incremento de las pruebas diagnósticas realizadas, de la estancia hospitalaria, de los costes y la administración de tratamientos antibióticos innecesarios o, en su caso, altas improcedentes en los casos de "bacteriemias ocultas" [2, 3, 9, 11].

La incidencia de bacteriemia comunitaria ha aumentado hasta 1-2/1.000 atenciones en los SU y a 6-10 episodios/1.000 ingresos hospitalarios desde dicho servicio [3, 12]. La etiología se debe a bacterias grampositivas en un 30-35%, gramnegativas en un 65-70% y anaerobios sobre el 1% [3, 6, 7, 12]. Esta proporción puede cambiar, si la incidencia de HC contaminantes fuera excesiva, a favor de las grampositivas [7]. En relación a las bacteriemias verdaderas (BV) o significativas, en cuanto al foco, la infección del tracto urinario con el 45-55% y el foco respiratorio (10-25%) son los más frecuentes. Mientras que la bacteriemia con foco desconocido se sitúa alrededor del 10% en el SU [3, 6, 7, 12]. De forma global, las bacterias aisladas con mayor frecuencia son *Escherichia coli, Staphylococcus aureus* y *Streptococcus pneumoniae* [3, 7, 12].

La mortalidad a los 30 días de los pacientes con HC positivos se ha cifrado entre 10-25% [3]. Ésta, se relaciona con la gravedad de la situación clínica (existencia de sepsis-shock séptico), el foco primario y las características de los pacientes (edad, comorbilidad, etc.) [3, 10-13].

Por todo ello, es muy importante la sospecha y confirmación de la BV, ya que ésta tiene un relevante significado diagnóstico, pronóstico y obligaría a cambiar algunas de las decisiones más importantes a tomar en el SU. Entre otras, indicar el alta o ingreso, extraer HC, administrar el antimicrobiano adecuado y precoz, etc. [1, 13]. En este sentido, conocer los factores predictivos de BV identificables en los SU que ayuden a evitar altas improcedentes e ingresos innecesarios, y sus consecuencias, se ha convertido en el objetivo de muchos autores [14, 17], que incluyen en sus estudios distintas variables clínicas, epidemiológicas y analíticas. Y, entre estas últimas, los biomarcadores de respuesta inflamatoria e infección (BMRII), ya que se ha demostrado que aumentan significativamente el rendimiento diagnóstico de los modelos predictivos propuestos inicialmente [18-21].

El objetivo de este estudio fue determinar qué factores identificables, de los que habitualmente son utilizados en la primera valoración en el SU, se relacionan con la predicción de bacteriemia en los HC extraídos en los pacientes atendidos por infección.

PACIENTES Y MÉTODOS

Diseño y sitio del estudio. Estudio observacional, retrospectivo, descriptivo y analítico de todos los HC extraídos en un SU de los pacientes adultos (≥18 años) atendidos por algún proceso infeccioso y que tras un seguimiento durante 30 días mantuvieron el diagnóstico de infección. Se realizó en un Hospital Universitario de tercer nivel de 786 camas perteneciente al Servicio de Salud de Castilla La Mancha (SESCAM).

Periodos del estudio y población incluida. Desde el 1 de enero de 2018 al 1 de julio de 2018 se incluyeron de forma consecutiva todos aquellos HC de pacientes diagnosticados clínicamente de un proceso infeccioso en el SU en los que también se habían registrado los signos vitales y muestras de analítica para realizar hemograma, bioquímica básica y BMRII [procalcitonina (PCT) y proteína C reactiva (PCR)]. Se excluyeron los pacientes de pediatría y de obstetricia-ginecología. La indicación de la solicitud de HC se llevó a cabo según el criterio del médico responsable.

Definiciones, técnicas y métodos establecidos para las muestras. La extracción de los HC se realizó por la técnica estándar por venopunción percutánea. En cada paciente se realizaron dos extracciones separadas entre sí en el tiempo (y asegurando que los sitios de venopunción eran diferentes). En el caso de sospecha de endocarditis se obtuvieron 3 parejas de HC. Por cada extracción (HC) se inocularon dos botellas (BD BACTEC®): una al medio aerobio y otra al anaerobio. Los HC se transportaron manualmente al servicio de microbiología para su procesamiento inmediato con el sistema automático de lectura Bactec/Alert® (BioMérieux, Durham, NC, EE.UU). El tiempo de incubación de los HC fue de 5-7 días, excepto en los casos de sospecha de endocarditis, brucelosis o a petición del médico responsable donde se prolongó hasta 30 días. Se definió como "bacteriemia verdadera (o significativa)" el aislamiento de bacterias habitualmente patógenas en uno o los dos HC con un cuadro clínico compatible. Y como "HC contaminado" ante el aislamiento en una sola botella de HC de *Staphylococcus* coagulasa-negativo, *Bacillus* spp, *Streptococcus viridans, Micrococcus* spp, *Propionibacterium* spp, *Corynebacterium* spp, y otros bacilos grampositivos cuando se interpretó la ausencia de significado clínico en estos casos (confirmado según la historia y/o el criterio del médico responsable y/o Microbiología). En otros casos, al existir 2 HC positivos y una significación

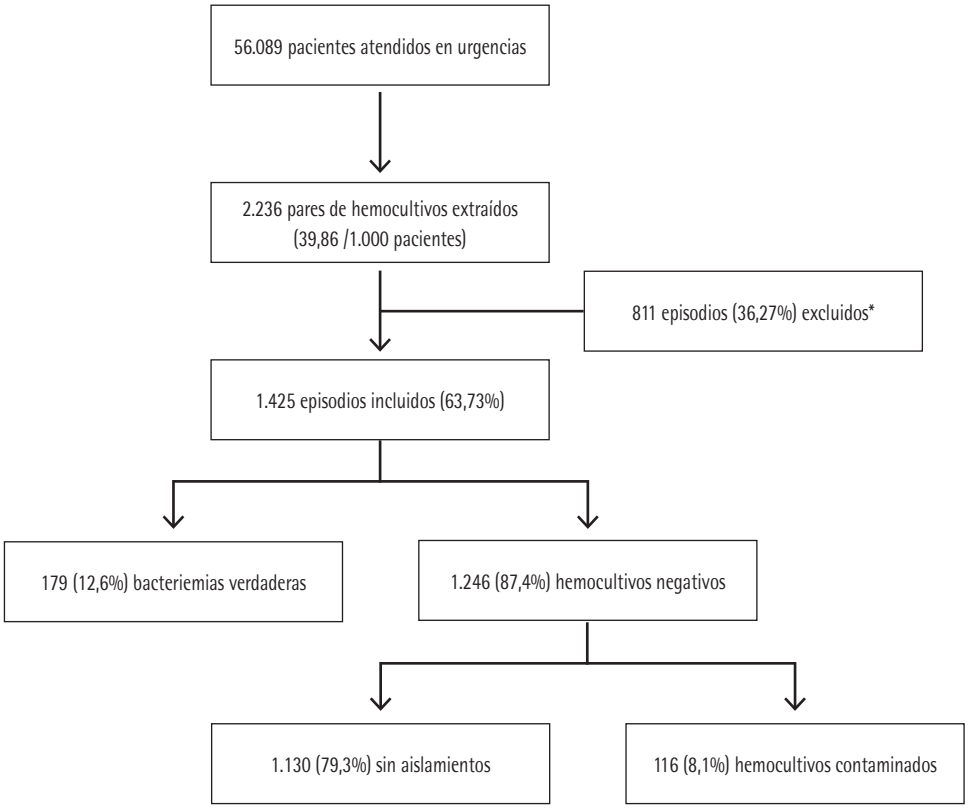


Figura 1 | **Diagrama de flujo de la inclusión de casos**

***Excluidos: Al no tener recogidos en la historia clínica las concentraciones de procalcitonina y proteína C reactiva obtenidas en el servicio de urgencias.**

clínica atribuida a ellos (especialmente en inmunodeprimidos o en portadores de catéteres vasculares o tras pruebas invasivas), sí se consideró BV y se trató con antibióticos.

Para los BMRII se adoptaron como valores de referencia los de nuestro laboratorio. Para la PCR de 0-8 mg/L y se determinó con un Método de inmunoanálisis enzimático cuantitativo (Slides VITROS CRP®) con una sensibilidad de 1 mg/L. Para la PCT se utilizaron como valores de referencia de la normalidad concentraciones <0,5 ng/mL, con método de inmunoanálisis cuantitativo de electroquimioluminiscencia ELECSYS (BRAHMS PCT®), que ofrece una sensibilidad de 0,02 ng/mL.

Variables recogidas. Se registraron sociodemográficas (edad, sexo, institucionalización), la toma de antibióticos en las 72 horas previas y/o los 3 meses anteriores, el ingreso en los 3 meses previos y la existencia de comorbilidades (enfermedad tumoral sólida u oncohematológica, hepatopatía, nefropatía, diabetes, enfermedad cardiaca crónica o cerebrovascular, enfermedad pulmonar obstructiva crónica, arterial periférica o del tejido conectivo e infección por el virus de la inmunodeficiencia humana). Se calculó el índice de Charlson [22] ponderado por la edad (y dicotomizado ≥3 puntos) y la situación funcional (índice de Barthel [23] y dicotomizado ≤60).

Se registraron datos clínicos y de gravedad: temperatura (T^a) en grados centígrados (°C), alteración de la consciencia definida con <15 puntos en la escala del coma de Glasgow (ECG), presión arterial sistólica (PAS), criterios de sepsis, sepsis grave o shock séptico y las variables que los definen según la conferencia de expertos de sepsis de 2001 [24]. También se aplicaron los criterios de selección pronóstica de pacientes en las definiciones del *quick Sepsis Related Organ Failure Assessment* (qSOFA) ≥2 y las variables que la constituyen según la tercera conferencia de consenso de sepsis (SEPSIS-3) [25]. Se incluyeron variables de evolución y destino: días de clínica previa, destino inicial de los pacientes, días de estancia hospitalaria, reconsulta en el SU en los 30 días posteriores y la mortalidad hospitalaria y a 30 días. En relación a las analíticas se registró el recuento de leucocitos (así como leucocitosis >12.000/mm^3, leucopenia <4.000/mm^3 o cayados >10%), concentración de PCR en mg/L (y dicotomizado para ≥9 mg/L y para ≥21 mg/L) y la de PCT en ng/mL (y dicotomizado para ≥0,5 ng/mL, para ≥1 ng/mL y para el punto de corte obtenido con mejor rendimiento según el índice de Youden).

Análisis estadístico. Para la asociación entre la confirmación de bacteriemia verdadera y las variables independientes

Tabla 1 **Características microbiológicas de la muestra global en función del tipo de aislamiento (bacteriemia verdadera frente a hemocultivos contaminados)**

Tipo de microorganismos	Total (N=295)	BACTERIEMIA VERDADERA [N=179 (61,1%)]	HEMOCULTIVOS CONTAMINADOS [N=116 (38,9%)]
Bacterias gramnegativas [98 (33,4 %)]			
Escherichia coli [n (%)]	61 (20,7)	61 (34,1)	0 (0,0)
Pseudomonas aeruginosa [n (%)]	8 (2,7)	8 (4,5)	0 (0,0)
Proteus spp [n (%)]	7 (2,4)	7 (3,9)	0 (0,0)
Klebsiella pneumoniae [n (%)]	5 (1,7)	5 (2,8)	0 (0,0)
Klebsiella spp [n (%)]	4 (1,4)	4 (2,2)	0 (0,0)
Salmonella spp [n (%)]	3 (1)	3 (1,7)	0 (0,0)
Serratia spp [n (%)]	3 (1)	3 (1,7)	0 (0,0)
Enterobacter spp [n (%)]	3 (1)	3 (1,7)	0 (0,0)
Otras gramnegativas[a] [n (%)]	4 (1,4)	4 (2,2)	0 (0,0)
Bacterias grampositivas [187 (63,1 %)]			
Streptococcus pneumoniae [n (%)]	35 (11,9)	35 (19,6)	0 (0,0)
Staphylococcus coagulasa-negativo [n (%)]	80 (27,2)	3 (1,7)	77 (66,5)
Propionibacterium spp [n (%)]	15 (5,1)	0 (0,0)	15 (12,9)
Micrococcus spp [n (%)]	14 (4,7)	0 (0,0)	14 (12,1)
Enterococcus spp [n (%)]	8 (2,7)	8 (4,5)	0 (0,0)
Staphylococcus aureus [n (%)]	8 (2,7)	8 (4,5)	0 (0,0)
SARM [n (%)]	6 (2)	6 (3,4)	0 (0,0)
Otras grampositivas [n (%)]	21 (7,1)	11 (6,1)	10 (8,6)
Bacterias anaerobias [10 (3,4 %)]			
Bacterioides spp [n (%)]	4 (1,4)	4 (2,2)	0 (0,0)
Clostridium spp [n (%)]	2 (0,7)	2 (1,1)	0 (0,0)
Otras bacterias anaerobias[c] [n (%)]	4 (1,4)	4 (2,2)	0 (0,0)

%: tanto por ciento (proporción referida a las columnas)
SARM *Staphylococcus aureus* resistente a meticilina
[a]Otras gramnegativas (4): *Haemophilus influenzae* (2) y *Neisseria meningitidis* (2)
[b]Otros grampositivos (11 bacteriemias verdaderas): *Streptococcus* spp (10) y *Listeria monocytogenes*.
Otros grampositivos (10 contaminantes): *Streptococcus* grupo *viridans*, *Staphylococcus hominis*, *Staphylococcus capitis*, *Staphylococcus capitis-capitis* y *Corynebacterium* spp.
[c]Otras bacterias anaerobias (4): *Prevotella* spp, *Fusobacterium* spp y *Veillonella* spp.

se utilizaron medias y sus desviaciones estándar (DE) para las cuantitativas y porcentajes para las cualitativas. Se utilizaron las pruebas de ji al cuadrado o exacta de Fisher, la t de Student y la U de Mann-Whitney, según fueran aplicables, para investigar la relación entre la existencia de BV frente a HC negativos (contaminados y los que no tuvieron ningún aislamiento) y las variables independientes (y aquellas que se dicotomizaron). Se consideró significativo un valor de $p<0,05$, los contrastes fueron bilaterales. Se realizó un análisis descriptivo (números absolutos y porcentajes) de ambos grupos (BV frente a HC negativos) en relación al tipo de patógeno encontrado globalmente y un análisis diferenciado según fuera el aislamiento de bacterias grampositivas, gramnegativas o anaerobias. Así como en función del foco o diagnóstico clínico realizado en el SU.

El estudio multivariante se realizó por un modelo de regresión logística (se eligió el método "introducir", que fuerza la inclusión de todas las variables elegidas del modelo que fueron

Tabla 2 **Foco/diagnóstico clínico de presunción en el servicio de urgencias de la muestra global en función de la existencia o no aislamientos en los hemocultivos**

Foco/diagnóstico clínico	Total (N=1.425)	BACTERIEMIA VERDADERA [N=179 (12,6%)]	HEMOCULTIVOS NEGATIVOS[a] [N=1.246 (87,4%)]
Infección del tracto urinario [n (%)]	470 (33,0)	88 (49,2)	382 (30,7)
Infección respiratoria [n (%)]	435 (30,5)	41 (22,9)	394 (31,6)
Fiebre sin foco claro [n (%)]	175 (12,3)	12 (6,7)	163 (13,1)
Infección abdominal [n (%)]	153 (10,7)	12 (6,7)	141 (11,3)
Infección piel y partes blandas [n (%)]	99 (6,9)	13 (7,3)	86 (6,9)
Infección del sistema nervioso central [n (%)]	47 (3,3)	7 (3,9)	40 (3,2)
Otros focos [n (%)]	46 (3,2)	6 (3,4)	40 (3,2)

%: tanto por ciento (proporción referida a las columnas)

Otros focos: Ginecológico, sospecha de endocarditis, por dispositivos externos.

[a]Hemocultivos negativos: incluye los 1.130 sin aislamiento y los 116 definidos como contaminados

aquellas que tuvieron significación estadística en el modelo univariable). Los resultados de las comparaciones se expresaron por los valores de p y las odds ratio (OR) con su intervalo de confianza del 95% (IC 95%), aceptándose como significativo un valor de p <0,05 o cuando el IC 95% de la OR excluye el valor 1.

La eficacia y capacidad de las variables independientes significativas y con interés clínico para predecir la existencia de BV frente a los HC negativos se estudió mediante el análisis de las curvas *Receiver Operating Characteristic* (ROC) con el intervalo de confianza (IC) del 95% del área bajo la curva (ABC) de la curva ROC y se comparó frente al valor neutro (0,5). Los errores estándar de las ABC se calcularon por métodos no paramétricos. Asimismo, se determinaron los puntos de corte en los valores de PCR y PCT con mayor capacidad diagnóstica que maximizaba la diferencia entre la tasa de verdaderos positivos y falsos positivos mediante el índice de Youden. Se valoró el rendimiento diagnóstico de las pruebas con los cálculos de la sensibilidad (S), la especificidad (E), el valor predictivo positivo (VPP) y el valor predictivo negativo (VPN), el coeficiente de probabilidad positivo (CP+) y negativo (CP–) para cada resultado estudiado, así como sus IC 95% por métodos binomiales exactos y por el de Taylor para los CP. El análisis estadístico se realizó con el paquete IBM-SPSS® Statistics 22 para Windows.

Consideraciones éticas. El estudio ha seguido todos los protocolos y normas de nuestro centro e internacionales (Declaración de Helsinki) para la utilización de los datos de los pacientes que se codificaron para asegurar la confidencialidad de los mismos. Se revisó la historia clínica informatizada y de atención primaria cuando se requirió. El estudio fue evaluado y aprobado por el Comité Ético de Investigación Clínica del Complejo Hospitalario Universitario de Toledo (referencia número 0398).

RESULTADOS

Durante el periodo de estudio se atendieron en el SU a 56.089 pacientes. Se realizaron 2.236 extracciones de HC, lo que supone 39,86 HC por cada 1.000 pacientes atendidos en el SU. De estos, finalmente sólo se incluyeron por oportunidad en el estudio a los 1.425 casos (63,73%), que cumplían con los criterios de inclusión señalados anteriormente. La edad media de los pacientes en los que se obtuvieron HC fue de 53 (DE 19) años con un rango entre 18 y 96 años. El 30,5% (434) tenían más de 65 años y el 53,3% eran mujeres (759). Del total de episodios, se consideraron como bacteriemias verdaderas 179 (12,56%) (6 de ellas polimicrobianas) y como HC negativos 1.246 (87,4%). Entre los considerados HC negativos se confirmaron 116 HC contaminados (8,14%). El diagrama de flujo de inclusión de episodios se muestra en la figura 1. Finalmente, cabe señalar que el 4,46% (8 casos) de las BV fueron dadas de alta desde el SU ("Bacteriemias ocultas").

La etiología agrupada y por microorganismos de las BV y de los HC contaminados se expone en la tabla 1. Entre los gramnegativos, el aislamiento más frecuente fue *E. coli* en 61 ocasiones (20,7%) y, por parte de los grampositivos, *S. pneumoniae* en 35 (11,9%). Asimismo, *E. coli* en 7 ocasiones (87,5%) también fue el patógeno más frecuente de las 8 bacteriemias ocultas. En relación con los HC contaminados los más frecuentes fueron *Staphylococcus* coagulasa-negativo (80 episodios, 27,2%).

El foco u origen clínico de presunción en el SU de las bacteriemias verdaderas y de los HC negativos se muestra en la tabla 2.

En la tabla 3 se muestran las características sociodemográficas, epidemiológicas, las comorbilidades, funcionales, clínicas, de gravedad, de evolución y destino de los pacientes. Al comparar los pacientes con BV y con HC negativos, solo se encontraron diferencias significativas en la edad, en la exis-

Tabla 3 **Características clínico-epidemiológicas, de evolución y destino de la muestra global y estudio univariable en función de la existencia o no de aislamientos en los hemocultivos**

	Total (N=1.425)	Valores perdidos	BACTERIEMIA VERDADERA [N=179 (12,6%)]	HEMOCULTIVOS NEGATIVOS[a] [N=1.246 (87,4%)]	Valor p
Datos demográficos-epidemiológicos					
Edad (años), media (DE)	52,76 (19,04)	0 (0,0)	56,20 (16,99)	52,27 (19,28)	0,010
Edad > 65 años [n (%)]	434 (30,5)	0 (0,0)	57 (31,8)	377 (30,3)	0,362
Género femenino [n (%)]	759 (53,3)	0 (0,0)	91 (50,8)	668 (53,6)	0,269
Institucionalizado [n (%)]	108 (7,6)	0 (0,0)	18 (10,1)	90 (7,2)	0,119
Toma de AB en 3 meses previos [n (%)]	409 (28,8)	0 (0,0)	59 (34,1)	350 (28,1)	0,062
Toma de AB en 72 horas previas [n (%)]	286 (29,2)	0 (0,0)	47 (27,2)	239 (19,2)	0,020
Ingreso en 3 meses previos [n (%)]	229 (16,1)	0 (0,0)	40 (22,3)	189 (15,2)	0,017
Comorbilidades					
Neoplasia sólida [n (%)]	73 (5,1)	3 (0,2)	23 (12,8)	50 (4)	0,001
Leucemia/Linfoma [n (%)]	42 (2,9)	3 (0,2)	8 (4,5)	34 (2,7)	0,147
Enfermedad hepática [n (%)]	40 (2,8)	3 (0,2)	4 (2,2)	36 (2,9)	0,422
Enfermedad cardiaca crónica [n (%)]	151 (10,6)	3 (0,2)	20 (11,2)	131 (10,5)	0,435
Enfermedad renal crónica [n (%)]	106 (7,4)	3 (0,2)	17 (9,5)	89 (7,1)	0,165
Enfermedad cerebrovascular [n (%)]	44 (3,1)	3 (0,2)	4 (2,2)	40 (3,2)	0,334
EPOC [n (%)]	157 (11)	5 (0,4)	12 (6,7)	145 (11,7)	0,055
Diabetes [n (%)]	217 (15,2)	3 (0,2)	32 (17,9)	185 (14,8)	0,172
Enfermedad arterial periférica [n (%)]	45 (3,2)	8 (0,6)	12 (6,7)	33 (2,7)	0,009
Enfermedad tejido conectivo [n (%)]	19 (1,3)	8 (0,6)	3 (1,7)	16 (1,3)	0,436
VIH [n (%)]	22 (1,6)	4 (0,3)	3 (1,7)	19 (1,5)	0,530
Índice de Charlsonb [media (DE)]	2,10 (2,30)	8 (0,6)	2,55 (2,35)	2,04 (2,28)	0,008
Índice de Charlson ≥ 3 [n (%)]	482 (34)	8 (0,6)	79 (44,6)	403 (32,5)	0,002
Índice de Barthel[c] [media (DE)]	93,50 (15,46)	12 (0,8)	93,45 (15,73)	93,51 (15,42)	0,962
Índice de Barthel ≤ 60 [n (%)]	80 (5,7)	12 (0,8)	7 (3,9)	73 (6,0)	0,272
Datos clínicos y de gravedad					
Temperatura en grados C [media (DE)]	38,11 (0,64)	0 (0,0)	38,35 (0,65)	38,06 (0,63)	0,015
Temperatura > 38,3°C [n (%)]	389 (27,3%)	0 (0,0)	90 (50,3)	299 (24,0)	<0,001
FC en lpm [media (DE)]	92,09 (12,13)	4 (0,30)	100,66 (16,83)	90,85 (11,05)	<0,001
FC > 90 lpm [n (%)]	707 (49,6)	4 (0,30)	131 (73,2)	576 (46,2%)	<0,001
FR en rpm [media (DE)]	22,00 (5,02)	73 (5,29)	27,57 (6,19)	21,24 (4,32)	<0,001
FR ≥ 22 rpm [n (%)]	636 (44,9)	73 (5,29)	135 (75,4%)	501 (40,4)	<0,001
Alteración de la consciencia ECG<15 [n(%)]	80 (5,7)	22 (1,54)	20 (11,3)	60 (4,9)	0,002
PAS en mmHg [media (DE)]	123,4 (19,8)	0 (0,0)	117,9 (21,3)	124,2 (19,5)	0,257
PAS < 100 mmHg [n (%)]	86 (6)	0 (0,0)	20 (11,2)	66 (5,3)	0,004
Criterios de sepsis (SRIS ≥ 2) [n (%)]	806 (56,6)	8 (0,60)	150 (83,8)	656 (52,6)	<0,001
Criterios de sepsis grave [n (%)]	103 (7,2)	8 (0,60)	25 (14,0)	78 (6,3)	0,001
Criterios de shock séptico [n (%)]	12 (20,8)	8 (0,60)	7 (3,9)	5 (0,4)	<0,001
qSOFA ≥ 2 [n (%)]	112 (8,0)	76 (5,33)	33 (18,6)	79 (6,5)	<0,001

Tabla 3 **Características clínico-epidemiológicas, de evolución y destino de la muestra global y estudio univariable en función de la existencia o no de aislamientos en los hemocultivos (cont.)**

	Total (N=1.425)	Valores perdidos	BACTERIEMIA VERDADERA [N=179 (12,6%)]	HEMOCULTIVOS NEGATIVOS[a] [N=1.246 (87,4%)]	Valor p
Datos de evolución y destino					
Días desde inicio de la clínica [media (DE)]	2,31 (1,29)	58 (4,1)	3,53 (1,50)	2,13 (1,15)	<0,001
Destino inicial de los pacientes [n (%)]	1425 (100,0)	0 (0,0)			<0,001
Alta	580 (40,7)	0 (0,0)	8 (4,5)	572 (45,9)	
Observación	418 (29,3)	0 (0,0)	49 (27,4)	369 (29,6)	
Planta de hospitalización	390 (27,4)	0 (0,0)	104 (58,1)	286 (23,0)	
Quirófano (Cirugía urgente)	22 (1,5)	0 (0,0)	12 (6,7)	10 (0,8)	
Unidad de Cuidados Intensivos	15 (1,1)	0 (0,0)	6 (3,4)	9 (0,7)	
Estancia hospitalaria en días [media (DE)]	2,86 (4,94)	0 (0,0)	10,87 (5,09)	1,71 (3,70)	<0,001
Reconsulta tras alta desde Urgencias [n (%)]	90 (6,3)	0 (0,0)	29 (16,2)	61 (4,9)	<0,001
Mortalidad intrahospitalaria [n (%)]	52 (3,6)	0 (0,0)	23 (12,8)	29 (2,3)	<0,001
Mortalidad a los 30 días [n (%)]	71 (5,0)	0 (0,0)	31 (17,3)	40 (3,2)	<0,001

%: tanto por ciento (proporción referida a las columnas); DE: desviación estándar; n: número; AB: antibióticos; h: horas; m: meses; EPOC: Enfermedad pulmonar obstructiva crónica; VIH: virus de la inmunodeficiencia humana; C: centígrados; FC: frecuencia cardiaca; lpm: latidos por minuto; FR: frecuencia respiratoria; rpm: respiraciones por minuto;

[a]Hemocultivos negativos: incluye los 1.130 sin aislamiento y los 116 definidos como contaminados

[b]Índice de Charlson: ponderado por la edad (se añade un punto al valor del índice de Charlson por cada década a partir de los 50 años) (referencia 22)

[c]Índice de Barthel (referencia 23)

Criterios de sepsis (SRIS ≥2) según conferencia de Consenso de 2001 (referencia 24)

Criterios de sepsis (qSOFA ≥2) según la tercera conferencia de consenso (Sepsis-3) (referencia 25)

tencia de neoplasia sólida, enfermedad arterial periférica y el índice de Charlson ponderado y dicotomizado (Índice de Charlson ≥3). También se encontraron diferencias significativas en la proporción de pacientes que habían tomado antibióticos en las 72 horas previas, así como en el antecedente de ingreso previo en los 3 meses anteriores, en ambos casos superior en los episodios de BV (p<0,05).

En relación con los datos de presentación clínica, tanto la T^a en °C (y dicotomizada >38,3°C), la frecuencia cardiaca (FC) (y >90 latidos por minuto), la frecuencia respiratoria(FR) (y ≥22 respiraciones por minuto) y la PAS <100 mmHg, junto con la existencia de los criterios clásicos de sepsis (dos o más criterios de síndrome de respuesta inflamatoria sistémica: SRIS ≥2), sepsis grave y shock séptico, además de un qSOFA ≥2, fueron significativamente superiores en los casos de BV.

En relación a la comparación de los valores analíticos (tabla 4) se encontraron diferencias significativas en el recuento absoluto de leucocitos, ante la existencia de una leucocitosis >12.000/mm^3 y una proporción >10% de cayados. Para la PCR existieron diferencias con mayores concentraciones medias en las BV y con puntos de corte ≥9 mg/L y ≥21 mg/L. Por último, al comparar los valores en los casos de BV con los HC negativos, para la PCT se obtuvieron las mayores diferencias entre concentraciones y también tanto con el punto de corte ≥0,43 ng/mL, como con un punto de corte ≥0,51 ng/mL y con PCT ≥1 ng/mL.

En la figura 2 se muestran las ABC-ROC de los BMRII (PCR y PCT). El ABC-ROC obtenida por la PCR para la predicción de bacteriemia fue de 0,629 (IC 95%: 0,584-0,675; p<0,01), siendo el punto de corte con mejor rendimiento diagnóstico encontrado cuando la PCR ≥21 mg/L, que consigue una S de 68,7%, E de 55,2%, VPP de 18,06%, VPN de 92,47%, CP+ de 1,53 y CP- de 0,56. Asimismo, el ABC-ROC obtenida por la PCT para la predicción de bacteriemia es de 0,963 (IC 95%: 0,950-0,975; p<0,001), siendo el punto de corte con mejor rendimiento diagnóstico PCT ≥ 0,51 ng/ml que consigue una S de 88,2%, E de 90,6%, VPP de 57,4%, VPN de 98,1%, CP+ de 9,38 y CP- de 0,13.

En la tabla 5 se muestran los resultados de las OR de las variables independientes significativas y con interés clínico para predecir la existencia de BV frente a los HC negativos en el estudio univariado y las que finalmente mantuvieron la significación estadística en el análisis multivariado, que fueron: la existencia de neoplasia sólida, una T^a > 38,3°C, una PAS < 100 mmHg, la existencia de criterios de shock séptico clásicos y una PCT ≥0,51 ng/ml.

La mortalidad cruda de los pacientes que ingresaron con BV a los 30 días fue del 17,3% (31 fallecidos), superior (p<0,001) a la de los casos de HC negativos del 3,2% (40 casos).

Finalmente, en los casos de bacteriemia oculta (8) la mortalidad a los 30 días fue del 50%, significativamente mayor al

Tabla 4 **Características analíticas de la muestra global y estudio univariable en función de la existencia o no aislamientos en los hemocultivos**

Hallazgos de laboratorio	Total (N=1.425)	Valores perdidos	BACTERIEMIA VERDADERA [N=179 (12,6%)]	HEMOCULTIVOS NEGATIVOS[a] [N=1.246 (87,4%)]	Valor p
Leucocitos por mm^3 [media (DE)]	11.348 (7.795)	0 (0,0)	16.198 (19.513)	10.652 (3.345)	<0,001
Leucocitosis > 12.000/ mm^3 [n (%)]	460 (32,3)	0 (0,0)	108 (60,3)	352 (28,3)	<0,001
Leucocitos < 4.000/ mm^3 [n (%)]	62 (4,4)	0 (0,0)	2 (1,1)	60 (4,8)	0,038
Cayados (bandas) > 10% [n (%)]	295 (20,7)	0 (0,0)	70 (39,1)	225 (18,1)	<0,001
Plaquetas por mm^3 [media (DE)]	206.841 (99.522)	0 (0,0)	216.917 (103.266)	205.393 (98.931)	0,148
Trombopenia < 100.000/mm^3 [n (%)]	107 (7,5)	0 (0,0)	12 (6,7)	95 (7,6)	0,399
Procalcitonina en ng/ml [media (DE)]	0,74 (3,09)	0 (0,0)	3,27 (5,92)	0,37 (0,22)	<0,001
Procalcitonina ≥ 0,43 ng/ml [n (%)]	332 (23,3)	0 (0,0)	164 (91,6)	168 (13,5)	<0,001
Procalcitonina ≥ 0,5 ng/ml [n (%)]	275 (19,3)	0 (0,0)	158 (88,3)	117 (9,4)	<0,001
Procalcitonina ≥ 1 ng/ml [n (%)]	158 (11,1)	0 (0,0)	125 (69,8)	33 (2,6)	<0,001
Proteína C reactiva en mg/l [media (DE)]	30,47 (28,71)	0 (0,0)	46,37 (40,95)	28,19 (25,71)	< 0,001
Proteína C reactiva ≥ 9 mg/l [n (%)]	1101 (77,3)	0 (0,0)	159 (88,8)	942 (75,6)	< 0,001
Proteína C reactiva ≥ 21 mg/l [n (%)]	681 (47,8)	0 (0,0)	123 (68,7)	558 (44,8)	< 0,001

%: tanto por ciento (proporción referida a las columnas)

DE: desviación estándar; n: número

[a]Hemocultivos negativos: incluye los 1.130 sin aislamiento y los 116 definidos como contaminados

resto. Todos ellos reconsultaron en el SU con ingreso posterior: 7 casos habían sido vistos por infección del tracto urinario (con aislamiento de *E. coli*) y uno por neumonía (*S. pneumoniae*). Cabe destacar que se objetivó en 3 de ellos (37,5%) la existencia de neoplasia sólida y una concentración de PCT > 0,51 ng/ml en los 8 episodios.

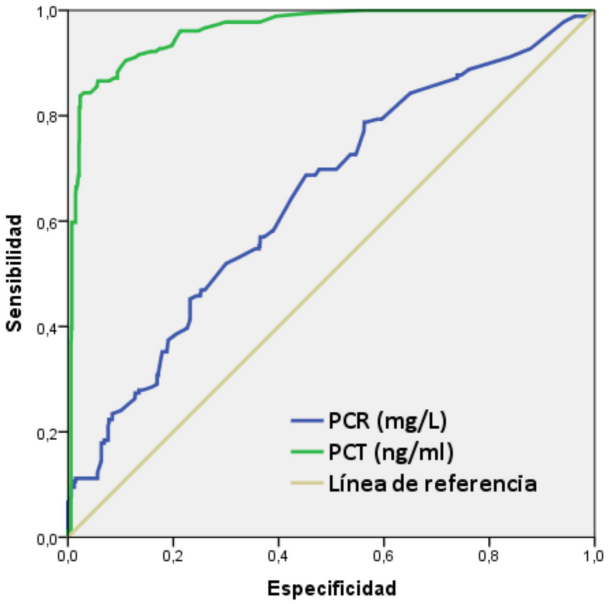
DISCUSIÓN

Si bien la técnica de extracción de los HC está bien estandarizada y protocolizada [2, 3, 6], todavía hay importantes controversias en relación a las indicaciones de cuándo hacerlo [1, 13, 17]. Comparadas con el resto de pruebas habituales que se realizan en los SU, requieren un mayor tiempo para su obtención, una buena técnica para evitar contaminaciones y carecen de utilidad diagnóstica definitiva inmediata [2, 3]. A pesar de ello, la obtención de HC es una práctica creciente en la valoración inicial de los pacientes con sospecha de infección en el SU [1, 3]. En ellos, la sospecha y confirmación de bacteriemia en el SU tiene un importante significado diagnóstico, pronóstico y terapéutico. Pero, además, los HC también se obtienen en el SU como garantía de continuidad asistencial, ya que del conocimiento de sus resultados dependerá el manejo posterior del paciente en su destino final. Porque, sin esta información obtenida al inicio de su atención, la evolución del enfermo podría ser distinta e incluso su mortalidad mayor [1, 19, 26].

Según los resultados de nuestro estudio, podemos confirmar que tras la valoración inicial urgente de los pacientes adultos con sospecha de infección grave, se han identificado distintos factores independientes relacionados significativamente con la confirmación de bacteriemia. Estos son: una concentración de PCT ≥0,51 ng/ml, la existencia de neoplasia sólida, una T^a >38,3°C, una PAS <100 mmHg o cuando se cumplen los criterios definitorios de shock séptico. Estos 5 factores, cuyo análisis y valoración se realiza fácil y habitualmente en los SU, constituyen una evidente aproximación predictiva de BV, por lo que al considerarlos, ayudarían a una mejor indicación de extracción de los HC, adecuación del tratamiento antibiótico y atención del paciente con sospecha de infección grave [1, 10, 17].

En este escenario clínico, en la última década, se ha acentuado el estudio de los factores predictores de bacteriemia [27] y se han propuesto distintos modelos predictivos para los SU de distinta complejidad [14-16, 28-32]. Cabe destacar el papel que los BMRII, y en especial la PCT, han adquirido en los últimos años como factores predictores independientes de bacteriemia [33, 34], con una capacidad diagnóstica incluso mayor que la de algunos modelos [19].

Shapiro et al. [15] publicaron su propuesta de modelo que clasifica el riesgo de bacteriemia en bajo (<1%), moderado (7-9%) y alto (15-26%) en función de unos criterios mayores (T^a >39,4°C, presencia de catéter vascular o sospecha de endocarditis) y de unos criterios menores (T^a >38,3°C, edad >65 años,



	ABC-ROC (IC 95%)	Valor de p
PCR (mg/L)	0,629 (0,584-0,675)	p<0,001
PCT (ng/ml)	0,963 (0,950-0,975)	p<0,001

Figura 2 | **Capacidad predictiva de bacteriemia de los biomarcadores**

ABC-ROC: Area Bajo la Curva – Receiver Operating Characteristic
IC 95%: intervalo de confianza al 95%
PCR: proteína C reactiva
PCT: procalcitonina

escalofríos, vómitos, PAS<90 mmHg, leucocitosis >18.000/mm^3, >5% cayados, trombopenia <150.000/mm^3 o creatinina >2 mg/dl). Éste, se ha convertido durante años, y tras ser validado [16], en una de las referencias más importantes para los SU [19]. Según este modelo de decisión, estaría indicada la extracción de HC cuando se cumpliera un criterio mayor o, al menos, dos menores. El modelo consigue una S del 94% y una E del 48%, con un ABC-ROC de 0,83. Sin duda, se trata de una escala con un rendimiento muy relevante, pero resulta laboriosa para su realización sistemática en los SU y no tiene en cuenta la indudable aportación que podrían hacer los BMRII [19]. Así, otra propuesta más sencilla, de Tudela et al. [14], que relacionó variables clínicas, analíticas y el índice de comorbilidad de Charlson, define dos variables significativas (índice de Charlson ≥2 y una PCT>0,4 ng/ml) con 1 y 2 puntos, respectivamente. Con ellas, se establecieron 4 grupos de probabilidad creciente de bacteriemia y obtenía un ABC de 0,80 y un VPN del 95,3% para "descartar" la existencia de bacteriemia. En este sentido, recientemente Contenti et al. [33] consiguen la misma ABC-ROC del modelo de Shapiro (0,83) con solo una variable de las definidas en nuestro estudio, la PCT, pero elevando el punto de corte de la PCT a concentraciones mayores de 2,25 ng/ml. También en esta línea, Tudela et al. [20] con un punto de corte >1 ng/ml de PCT consigue una ABC-ROC de 0,80 y S: 64%, E: 84% y un VPN de 94%. Es decir, que la inclusión de la PCT en cualquier modelo o como factor individual, hoy en día, debería ser considerada en los SU [10, 18-21, 33, 34]. En nuestro estudio, la PCT es el factor que mayor peso predictivo consigue con una OR de 4,52 (4,21-4,84) y una ABC-ROC de 0,96 con un punto de corte de PCT ≥0,51 ng/ml, así como un VPN de bacteriemia del 98%.

Otros modelos recientes, que incluyen algunos de los factores identificados en nuestro estudio, aunque útiles, no consiguen alcanzar el rendimiento del modelo de Shapiro [15]. Pero algunos de ellos son más fáciles de evaluar e implementar en el SU [28, 32]. Precisamente, que el modelo o los factores evaluados sean sencillos y rápidos de realizar en el SU, ha sido señalado en recientes metaanálisis y revisiones [29, 30]. Aunque, paradójicamente, se ha comprobado que ninguno de los 15 modelos de dichas revisiones se han implementado en la práctica clínica diaria por sus respectivos autores [30].

Un estudio multicéntrico define un modelo que incluye T^a ≥38°C, plaquetas <150.000/mm^3 y una puntuación <15 de la ECG. Con él se obtiene un ABC de 0,68 [32]. En otro estudio, Su et al. [28], incluye como variables la T^a ≥38,3°C, taquicardia ≥120 lpm, linfopenia <500/mm3 y otros datos analíticos. Entre ellos, una PCT >0,5 ng/ml (ésta con OR de 3,14, algo menor a nuestros datos, pero de las más importantes del modelo). Este modelo de Su et al. consigue un ABC-ROC de 0,85 [28].

Por contra, otro metaanálisis [29] que revisa 35 estudios no ha sido capaz de identificar los factores independientes predictores de bacteriemia. Por ello, en él no se recomienda la

Tabla 5 **Se muestran los resultados de las Odds Ratio de las variables significativas en el estudio univariado y mutivariado**

	ANÁLISIS UNIVARIADO		ANÁLISIS MULTIVARIADO	
Variable	OR (IC 95%)	Valor p	OR (IC 95%)	Valor p
AB en los 3 días previos	1,572 (1,093-2,261)	0,006		
Ingreso en los 3 meses previos	1,609 (1,096-2,363)	0,015		
Neoplasia sólida	3,527 (2,094-5,939)	<0,001	1,738 (1,271-2,205)	<0,001
Enfermedad arterial periférica	2,653 (1,344-5,238)	0,008		
Índice de Charlson ≥ 3	1,674 (1,217-2,304)	0,002		
Temperatura > 38,3°C	3,203 (2,324-4,413)	<0,001	1,600 (1,299-1,901)	<0,001
PAS < 100 mmHg	2,249 (1,328-3,809)	0,004	3,684 (2,785-4,583)	<0,001
FC > 90 lpm	3,175 (2,239-4,500)	<0,001		
FR > 22 rpm	4,520 (3,157-6,469)	<0,001		
ECG < 15 puntos	2,476 (1,453-4,218)	0,001		
Criterios de sepsis (SRIS ≥ 2)	4,652 (3,079-7,030)	<0,001		
Criterios de sepsis grave	2,431 (1,503-3,932)	<0,001		
Criterios de shock séptico	10,101 (3,171-32,179)	<0,001	2,961 (1,783-4,139)	0,012
qSOFA ≥ 2	3,307 (2,126-5,143)	<0,001		
Leucocitosis > 12.000/ mm^3	3,863 (2,795-5,341)	<0,001		
Cayados (bandas) > 10%	2,914 (2,089-4,066)	<0,001		
Procalcitonina ≥ 0,43 ng/ml	70,156 (40,350-121,978)	<0,001		
Procalcitonina ≥ 0,51 ng/ml	72,602 (44,325-118,916)	<0,001	4,523 (4,206-4,840)	<0,001
Procalcitonina ≥ 1 ng/ml	80,735 (50,540- 128,970)	<0,001		
Proteína C reactiva ≥ 9 mg/l	2,566 (1,583-4,157)	<0,001		
Proteína C reactiva ≥ 21 mg/l	2,708 (1,937-3,786)	<0,001		

OR: Odds ratio; IC 95%: intervalo de confianza del 95%; C: centígrados; PAS: presión arterial sistólica; FC: frecuencia cardiaca; FR: frecuencia respiratoria; ECG: escala del coma de Glasgow; SRIS: síndrome de respuesta inflamatoria sistémica; qSOFA: *quick Sepsis Related Organ Failure Assessment*

extracción de HC sistemáticamente solo con fiebre y leucocitosis. Y sugiere que se debe continuar buscando un modelo ideal que incorpore otras variables como los BMRII y la valoración clínica de la gravedad del paciente (con los signos vitales: T^a, FC, FR, PAS y nivel de consciencia) [19, 29].

Precisamente, la T^a >38,3°C, la PAS<100 mmHg, la existencia de shock séptico (hipotensión que no remonta con fluidoterapia y precisa agentes vasoactivos) son, junto a la existencia de neoplasia sólida, los factores identificados por nuestro estudio junto con la PCT. Por ello, creemos que la confección de un sencillo modelo con ellos y/o la consideración de aquellos pacientes con T^a>38,3°C, hipotensión y/o una PCT ≥0,51 ng/ml, debería hacer al clínico plantearse la existencia de una BV. Y, consecuentemente, indicar la obtención de HC junto con el tratamiento adecuado a cada paciente.

Nuestro estudio tiene distintas limitaciones que hay que señalar. En primer lugar, se trata de un estudio unicéntrico y retrospectivo, donde la indicación de conseguir HC se realiza según las decisiones del médico responsable. Por ello, junto a esta variabilidad clínica, hay que recordar que un 36,27% de los HC no se registraron por no cumplir los criterios de inclusión (al no tener datos de la PCR y PCT), todo ello podría suponer un sesgo de selección al no haber sido considerados todos los episodios. Además, la selección de variables clínicas podría haber sido más completa (no se incluyeron variables como escalofríos, tiritona, náuseas-vómitos, etc.) [25, 26, 35]. También hay que señalar la importante tasa de HC contaminantes (8,14%), lo que no supone un obstáculo para analizar nuestros resultados, como ya ha sido publicado previamente [7]. No obstante, a pesar de estas limitaciones, creemos que los resultados representan un fiel reflejo de la realidad y epidemiología de nuestro SU, pero no se pueden extrapolar y carecen de validez externa. De manera que sería necesario realizar un estudio multicéntrico y prospectivo para poder confirmar estos hallazgos.

En conclusión, en el paciente con sospecha de infección

grave en el SU, la existencia de concentraciones de PCT ≥0,51 ng/ml (como se ha sugerido recientemente [19]) junto con una temperatura >38,8°C y la valoración de la gravedad clínica (hipotensión y/o ante la existencia de criterios de shock séptico), nos obligaría a descartar la existencia de una BV (independientemente del foco). Y así, a obtener HC y aplicar el tratamiento adecuado y precoz que precise el enfermo. Además, en los casos donde exista el antecedente de neoplasia sólida, deberíamos ser menos restrictivos para indicar la extracción de los HC ante el mayor riesgo de bacteriemia.

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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 Scientific Biomarkers, B.R.A.H.M.S. AG y Biomerieux.

Los autores declaran la ausencia de conflictos de intereses en relación con el presente artículo.

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Micafungin as antifungal prophylaxis in non-transplanted haemotological patients

Teresa Villaescusa[1]
Lourdes Vázquez[2]
Juan Miguel Bergua[3]
Julio García[4]
Antonio Romero[5]
M. Teresa Olave[6]
Daniel García Belmonte[7]
M. Paz Queipo de Llano[8]
Grupo de Infecciones en pacientes hematológicos. Sociedad Andaluza de Hematología y Hemoterapia.

[1]Hospital Virgen de la Concha, Zamora.
[2]Hospital Clínico Universitario, Salamanca.
[3]Hospital San Pedro de Alcántara, Cáceres.
[4]Hospital Universitario Príncipe de Asturias, Madrid.
[5]Complejo Hospitalario Universitario, Granada.
[6]Hospital Clínico Lozano Blesa, Zaragoza.
[7]Hospital Universitario de La Zarzuela, Madrid.
[8]Hospital Virgen de la Victoria, Málaga.

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ABSTRACT

Introduction. Fungal infections are a major cause of morbidity and mortality in the haematological patients. These infections are mainly due to *Candida* spp. and *Aspergillus* spp. Mortality by these infections is high, but rates have descended in the latest series due to better antifungal agents. Echinocandins are, *in vitro,* very active against *Candida* and *Aspergillus* spp. The objective of the study is to analyse the efficacy and safety of micafungin in the antifungal prophylaxis of haematological patients on chemotherapy.

Material and methods. A multicentre, observational retrospective study was performed in 7 Haematology Departments in Spain. Patients admitted to these departments with chemotherapy or immunosuppressive treatment, and who had received antifungal prophylaxis with micafungin between 1 January 2009 and 31 December 2014 were included.

Results. There were 5 cases of probable or proven fungal infection (4.8%) according to the 2008 EORTC criteria: 2 proven, 3 probable. The types of fungal infection were 3 aspergillosis and 2 candidiasis. There were no drop-outs from the prophylaxis with micafungin due to toxicity.

Conclusion. Micafungin is an antifungal agent which, used in prophylaxis, has demonstrated good efficacy and an excellent toxicity profile, making it an apparently interesting option in patients requiring antifungal prophylaxis during their hospitalisation episode.

Key words: fungal, *Aspergilllus*, prophylaxis, toxicity, echinocandins.

Correspondence:
Teresa Villaescusa de la Rosa.
Hospital Virgen de la Concha. Avda. Requejo nº 35. 49022. Zamora.
E-mail: tvillaescusa@saludcastillayleon.es

Micafungina como profilaxis antifúngica en pacientes hematológicos no trasplantados

RESUMEN

Introducción. Las infecciones fúngicas son una importante causa de morbilidad y mortalidad en los pacientes hematológicos. Estas infecciones son principalmente debidas a *Candida* spp.y *Aspergillus* spp. La mortalidad debida a estas infecciones es alta, pero ha descendido a lo largo de las últimas series gracias a los mejores agentes antifúngicos. Las equinocandinas son, in vitro, muy activas contra *Candida* y *Aspergillus* spp. El objetivo de este estudio es analizar la eficacia y seguridad de micafungina en la profilaxis antifúngica de pacientes hematológicos en tratamiento quimioterápico.

Material y métodos. Un estudio multicéntrico, observacional, retrospectivo se llevó a cabo en 7 servicios de Hematología en España. Se incluyeron los pacientes ingresados con quimioterapia o tratamiento inmunosupresor que hubieran recibido micafunfina como profilaxis entre el 1 de enero de 2009 y el 31 de diciembre de 2014.

Resultados. Hubo 5 casos de infección fúngica probable o probada (4,8%) según los criterios de la EORTC de 2008: 2 probadas, 3 probables. Las infecciones fúngicas fueron 3 aspergilosis y 2 candidiasis. No hubo ningún abandono de la profilaxis con micafungina debido a toxicidad.

Conclusión. Micafungina es un agente antifúngico que, usado en profilaxis, ha demostrado buena eficacia y excelente perfil de toxicidad, siendo una opción interesante en pacientes que requieren profilaxis antifúngica durante su hospitalización.

Palabras clave: hongos, *Aspergilllus*, profilaxis, toxicicidad, equinocandinas.

INTRODUCTION

Fungal infections are a major cause of morbidity and mortality in haematological patients, particularly in at high risk of fungal infection patients [1, 2]. The increase in the number of individuals with some type of immunosuppression, is the most important cause in the increase of this type of infections. Approximately 10% -50% of haematological patients with marked neutropenia or recipients of a haematopoietic stem cell transplant have an episode of Invasive Fungal Infection (IFI) during the evolution of their disease. These infections are mainly due to *Candida* spp. and *Aspergillus* spp. [2-4]. Mortality by these infections is usually high, due to the difficulty involved in making an early diagnosis. Fortunately, mortality rates for aspergillosis have gradually descended in the latest series and this is fundamentally due to two important breakthroughs. On the one hand, the improvement in early diagnostic techniques, such as galactomannan, aspergillus PCR and imaging techniques. On the other hand, the advent of antifungal agents with greater efficacy and good tolerance used for prophylactic, empirical, pre-emptive and targeted treatment [5, 6]. Echinocandins are very active in vitro against *Candida* and *Aspergillus* spp. [7], which have proven their efficacy in the prophylaxis of fungal infection [8]. Micafungin, as opposed to the other echinocandins, presents a better activity against certain strains of *Candida* spp., classically *Candida glabrata* [7, 9] and also against *Aspergillus* spp. [8, 10]. It has a low potential for drug interactions [11-14], which could make it interesting in the case of patients requiring concomitant medication and it can be given to patients with moderate liver failure in whom the azoles, the reference drugs in prophylaxis, have certain limitations [15]. This is why there are consensus-based documents that point to the advantages of this drug in prophylaxis [16]. There is published experience with micafungin in the primary prophylaxis of haematological patients in the context of haematopoietic stem cell transplant and acute myeloid leukaemias induction therapy [17, 18]. International guidelines provide a recommendation for micafungin, both in prophylaxis and in the treatment of the candidiasis [4, 19-21]

Some Spanish centres have accumulated experience in primary prophylaxis with micafungin in patients admitted to haematology departments undergoing chemotherapy in whom a prolonged period of neutropenia is expected and in whom azoles might constitute a problem of tolerability due to drug interactions, liver alterations, long QT syndrome or intolerance. There is a great deal of experience published with micafungin in the antifungal prophylaxis of patients undergoing haematopoietic stem cell transplant [22-26]. However, experience is more limited in non-transplanted patients. Therefore, the evaluation of the efficacy and safety of antifungal prophylaxis with micafungin in haematological patients undergoing chemotherapy is an interesting area of investigation, and therefore we are proposing a retrospective analysis of patients undergoing chemotherapy who have received prophylactic antifungal treatment with micafungin. The objective of the study is to analyse the efficacy and safety of micafungin in the antifungal prophylaxis of haematological patients on chemotherapy.

MATERIAL AND METHODS

A multicentre, observational retrospective study was performed in 7 Haematology Departments in Spain. All the patients admitted to these departments that had received chemotherapy or immunosuppressive treatment for their haematological disease and who had received antifungal prophylaxis with micafungin over 5 consecutive days in the period comprised between 1 January 2009 and 31 December 2014 were included. Each patient's observation period ended when they were discharged for any reason. Micafungin was administered intravenously at a dose of 50 mg a day.

The data were obtained from the patients' health history by means of a case report form (CRF) requested from the Alce Ingenieria company, whereas the SPSS statistical application was used for the statistical analysis.

The possible, probable or proven fungal infection criteria were consistent with those described by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) of 2008 [27].

The objective was to analyse the efficacy and safety of micafungin in the antifungal prophylaxis of haematological patients on chemotherapy. The efficacy of antifungal prophylaxis was defined as the absence of diagnosed or suspected fungal infection during the prophylaxis period with micafungin. For this purpose, the daily dose used, the days of prophylaxis, the reason for the end of treatment, the need to change the anti-fungal agent or the dose of micafungin, the reasons for the change, as well as the results of the different diagnostic tests performed such as cultures, serologies or radiological tests, were analysed. With regard to safety, micafungin's tolerability and safety were analysed on the basis of adverse reactions recorded in the medical history as being attributable to the treatment with micafungin, as well as the degree of the adverse reaction.

RESULTS

A total of 104 episodes corresponding to 89 haematological patients from 7 hospitals in Spain were analysed. The patients' baseline characteristics can be observed in table 1. The median patient age was 59 years (range 19-84), 55 were men and 34 were woman. The patients presented the following haematological diseases: Forty-three episodes of acute myeloid leukaemia (41.3%), thirty-one episodes of acute lymphoblastic leukaemia (29.8%), ten episodes of lymphoma (9.6%), nine episodes of aplastic anemia (8.7%) and eleven episodes of other haematological conditions (10.6%). The median of days of hospitalisation for the episodes was 31.5 days. In 63 episodes reported (60.6%), micafungin was given as prophylaxis following the diagnosis. It should be emphasised that in 19 episodes (18.3%), the patients were in relapse, partial response

Table 1 Patients' baseline and demographic characteristics

Age [median (range)]: 59 years (19-84 years)	
Sex	
Male: 55 patients (61.8%)	
Female: 34 patients (38.2%)	
Haematological disease	
Acute myeloblastic leukaemia: 43 episodes (41.3%)	
Acute lymphoblastic leukaemia: 31 episodes (29.8%)	
Lymphoma: 10 episodes (9.6%)	
Bone marrow aplasia: 9 episodes (8.7%)	
Others: 11 episodes (10.6%)	
Situation of the disease	
Diagnosis: 63 patients (60.6%)	
Complete remission: 20 patients (19.2%)	
Partial response: 7 patients (6.7%)	
Relapse: 11 patients (10.6%)	
Salvage: 0 patients (0%)	
Resistant: 1 patient (1%)	
Unknown: 2 patients (1.2%)	
Total: 104 episodes	
Days´ hospitalisation: 31.5 days (range 4-451)	

Table 2 Reasons for the use of micafungin. (More than one reason could be chosen).

Prophylaxis	95
Protocol	13
Failure of previous antifungal	2
Limiting drug interactions	4
Liver dysfunctions	15
Severe mucositis	7
Long QT syndrome	1
Other reason	31

Table 3 Reasons for ending prophylaxis with micafungin in 101 of the 104 total episodes.

End of prophylaxis	65 (64.4%)
Adverse reaction	0 (0%)
Empirical treatment	19 (18.8)
Change of antifungal	7 (6.9%)
Other	10 (9.9%)
Total	101 evaluable episodes

Table 4 Development of fungal infection

Probable or proven fungal infection	
NO	99 episodes (95.2%)
YES	5 episodes (4.8%)
Total	104 episodes
EORTC criteria	
Probable	3 (60%)
Proven	2 (40%)

EORTC : European Organization for Research and Treatment of Cancer

or resistant; in other words, with uncontrolled haematological disease.

In most of the episodes (95) micafungin was the selected drug as prophylaxis because of the center practice. Some of the other reasons for the choice were drug interactions with the use of other antifungals (4), liver dysfunctions (15), severe mucositis (7) or long QT syndrome (1). The results are displayed in greater detail in table 2.

The median days of use of micafungin was 18 days (range 5-384) at a dose of 50 mg/day. We have data from 101 of the 104 episodes with regard to the reason for the end of prophylaxis. There were no drop-outs from the prophylaxis with micafungin due to toxicity, and the prophylaxis was finished when the neutropenia period ended in 64.4% of the cases. Empirical antifungal treatment was initiated in 19 episodes (18.8%), the antifungal was changed on 7 occasions, and in 10 cases the prophylaxis was finished for other reasons .The data are shown in table 3. 91 of the 104 episodes (87.5%) presented neutropenia (<500 neutrophils/mm^3), with a median duration of 22 days. There were 59 episodes of fever (56.7%) and 45 episodes (43.3%) without fever during hospitalisation. There were 5 cases of probable or proven fungal infection (4.8%) according to the 2008 EORTC criteria: 2 proven and 3 probable. We have eliminated 4 possible fungal infections because probably there are not an IFI. The types of fungal infection were 3 probable aspergillosis and 2 proven candidiasis. The data are shown in table 4. Of the 26 patients that needed to start empirical antifungal treatment or a change of antifungal, probable or proven fungal infection according to the EORTC criteria was only confirmed in 5 cases (19.2%). In other words, 80,8% of the patients who were switched from micafungin to other antifungals did not ultimately develop an IFI. Twelve (11.7%) of the 89 patients recruited to the study died, although only 2 of them were diagnosed with fungal infection. 88.3% of the cases were discharged due to clinical improvement.

DISCUSSION

Fungal infections are a serious complication in haematological patients and are associated with a high rate of mortality. One of the most commonly used strategies is prophylaxis in patients at risk. The azoles are the drugs that have been used most in prophylaxis in haematological patients. However, we know that they have a toxicity profile that renders them incompatible with other drugs or the patients' clinical situations. For this purpose, other families of drugs that may be used in prophylaxis are needed. Of all the requirements that a prophylactic drug must meet, one of the most important ones is good efficacy, but the drugs must be safe and easy to administer. Micafungin is an agent that is widely used in the haematological population for the prevention of IFI. There are works involving prophylaxis with micafungin in homogeneous populations of patients, such as in acute induction leukaemias. It has been compared to posaconazole in patients with acute leukaemias and myelodysplastic syndromes on induction treatment in a randomised study, proving to be a safe prophylactic alternative in this type of patients [28]. It has also been compared to fluconazole and traconozole in patients undergoing haploidentical transplantation, presenting good efficacy [29]. We also have data from a meta-analysis performed with 1,049 cases and 959 controls, confirming that micafungin had a significantly higher treatment success rate than the other antifungals, with a better secure profile [30]. However, there are no published data with more heterogeneous patient populations in real practice. This study shows one of the largest populations studied to date on prophylaxis with micafungin. The incidence of probable or proven invasive fungal infection in our study population is 4,8%, similar to that which is published in other series [2-4], particularly considering that a large part of the population of our study were high-risk patients diagnosed with acute leukaemias. In most of these cases, the causal agent was *Aspergillus* spp, although none of the proven IFI were caused by this fungus, but rather by *Candida* spp. With regard to drug safety, it was a drug with an excellent toxicity profile that did not require any withdrawals due to toxicity. What is more, in some cases it was the drug of choice after toxicity by previous prophylaxis.

This study has important limitations, particularly on account of its retrospective nature. Similarly, the patients are very heterogeneous, although we consider this to be part of our hospitals' daily practice. New prospective studies in different haematological populations would be very interesting in order to confirm these data.

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CONFLICT OF INTEREST

None to declare

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Chronic obstructive pulmonary disease (COPD) in Spain and the different aspects of its social impact: a multidisciplinary opinion document

Emilio Bouza[1,2]
Agustí Alvar[1,3]
Pere Almagro[4]
Tamara Alonso[5]
Julio Ancochea[5,6]
Ferrán Barbé[1,7]
Josep Corbella[8]
Diego Gracia[9]
Enrique Mascarós[10]
Joan Melis[11]
Marc Miravitlles[12]
Mariano Pastor[13]
Patricia Pérez[14]
David Rudilla[15]
Antoni Torres[1,3,16]
Joan Bautista Soriano[5,17]
Antoni Vallano[18]
Franciso Vargas[19]
Esteban Palomo[20]

[1]CIBER de Enfermedades Respiratorias (CIBERES CB06/06/0058), Spain.
[2]Fundación Ciencias de la Salud. Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Medicine Department, School of Medicine, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid. Spain.
[3]Respiratory Institute. Hospital Clinic, University of Barcelona IDIBAPS.
[4]Chronic Patients Unit. Hospital Universitario Mútua de Terrassa. Barcelona. Spain.
[5]Pneumology Department. Hospital de la Princesa. Universidad Autónoma. Madrid. Spain.
[6]Coordinator "Estrategia epoc del Sistema Nacional de Salud". Spain
[7]Institut de Recerca Biomédica de Lleida. Lleida. Spain
[8]La Vanguardia. Barcelona. Spain
[9]Fundación Ciencias de la Salud. Department of Prevention and Public Health. School of Medicine, Universidad Complutense de Madrid. Spain
[10]Department of Family and Community Medicine, Hospital Dr Peset. Specialist in family and community medicine Centro de Salud Fuente de San Luis. Valencia. Spain.
[11]Institute Clinic Respiratory. Hospital Clinic. Barcelona. Spain
[12]Department of Peumology. Hospital Universitari Vall d'Hebron/Vall d'Hebron Institut de Recerca (VHIR). Barcelona. Spain
[13]Asociación Alfa-1. Spain.
[14]Advanced Practice. Hospital de la Princesa. Universidad Autónoma de Madrid. Madrid. Spain.
[15]Patient care. Air Liquide Healthcare. Madrid. Spain
[16]Servei de Pneumologia. Hospital Clinic. Universitat de Barcelona. IDIBAPS. CIBERES. Barcelona. Spain
[17]Department of Medicine. Universidad Autónoma de Madrid. Madrid. Spain
[18]Catalan Health Service (CatSalut). Barcelona. Spain. Department of Pathology and Experimental Therapeutics. University of Barcelona. Spain.
[19]Subdirección General de Calidad e Innovación. Dirección General de Salud Pública, Calidad e Innovación. Ministerio de Sanidad, Consumo y Bienestar Social. Madrid. Spain
[20]Fundación Ciencias de la Salud. Madrid. Spain.

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases in the World, and one of the most important causes of mortality and morbidity. In adults 40 years and older, it affects more than 10% of the population and has enormous personal, family and social burden. Tobacco smoking is its main cause, but not the only one, and there is probably a genetic predisposition that increases the risk in some patients. The paradigm of this disease is changing in Spain, with an increase of women that has occurred in recent years. Many of the physiopathological mechanisms of this condition are well known, but the psychological alterations to which it leads, the impact of COPD on relatives and caregivers, the limitation of daily life observed in these patients, and the economic and societal burden that they represent for the health system, are not so well-known. A major problem is the high under-diagnosis, mainly due to difficulties for obtaining, in a systematic way, spirometries in hospitals and health-care centers. For this reason, the Fundación de Ciencias de la Salud and the Spanish National Network Center for Research in Respiratory Diseases (CIBERES) have brought together experts in COPD, patients and their organizations, clinical psychologists, experts in health economics, nurses and journalists to obtain their opinion about COPD in Spain. They also discussed the scientific bibliometrics on COPD that is being carried out from the CIBERES and speculated on the future of this condition. The format of the meeting consisted in the discussion of a series of questions that were addressed by different speakers and discussed until a consensus conclusion was reached.

Keywords: COPD, Chronic Obstructive Pulmonary Disease, Psychological impact, Health-Care burden, Health Economics, Spirometry, Research bibliometrics, Patients organizations

Correspondence:
Emilio Bouza MD, PhD
Instituto de Investigación Sanitaria Gregorio Marañón
C/ Dr. Esquerdo, 46 - 28007 Madrid, Spain
Phone: +34- 91- 586 84 53/Fax: +34- 91- 504 49 06
E-mail: emilio.bouza@gmail.com

Esteban Palomo, PhD
Director. Fundación de Ciencias de la Salud.
C/ Severo Ochoa, 2, - 28760 Tres Cantos. Madrid
Phone +34 91 3530150

Enfermedad Pulmonar Obstructiva Crónica (EPOC) y diferentes aspectos de su impacto social: Un documento multidisciplinar de opinión

RESUMEN

La enfermedad pulmonar obstructiva crónica (EPOC) es una de las enfermedades más prevalentes en el mundo y una de las causas más importantes de mortalidad y morbilidad. En los adultos de más de 40 años, afecta al menos al 10% de la población y tiene una enorme carga personal, familiar y social. El tabaquismo es su principal causa, pero no la única, y probablemente existe una predisposición genética que aumenta el riesgo en algunos pacientes. El paradigma de esta enfermedad está cambiando en España, con un aumento de la incidencia en mujeres que se ha producido en los últimos años. Muchos de los mecanismos fisiopatológicos de la EPOC son bien conocidos, pero no lo son tanto las alteraciones psicológicas a las que conduce, el impacto de la enfermedad en los familiares y cuidadores, la limitación de la vida cotidiana que se observa en estos pacientes y la carga económica y social que representan para el sistema sanitario. Un problema importante es el elevado infra-diagnóstico, debido principalmente a las dificultades para obtener, de forma sistemática, espirometrías en los hospitales y centros de salud. Por este motivo, la Fundación de Ciencias de la Salud y el Centro de Investigación en Enfermedades Respiratorias (CIBERES) han reunido a expertos en EPOC, pacientes y sus organizaciones, psicólogos clínicos, expertos en economía de la salud, enfermeras y periodistas para obtener su opinión sobre la EPOC en España. También se ha hablado de la bibliometría científica sobre la EPOC que se está llevando a cabo desde el CIBERES y se ha especulado sobre el futuro de esta enfermedad. El formato de la reunión consistió en la discusión de una serie de cuestiones que fueron abordadas por diferentes ponentes y discutidas hasta llegar a una conclusión consensuada.

Palabras clave: Enfermedad Pulmonar Obstructiva Crónica, Impacto psicológico, Carga de trabajo, Atención sanitaria, Economía de la Salud, Espirometría, Investigación bibliométrica, Organizaciones de pacientes

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most frequent causes of morbidity and death in the World, and in Spain. Chronic inhalation of toxic fumes, particularly from tobacco smoke, is the most common causal risk factor, but not the only one. COPD usually appears in its most severe and symptomatic forms after the age of 65, considerably diminishing quality of life and the possibility of having an independent, autonomous life.

The available scientific information on COPD is vast, particularly biomedical information on COPD. However, data regarding other aspects, such as: the impact in the daily life of patients, the experience of care-givers, the economic impact in the health-care system and the attention from the mass-communication media to this problem, have received less attention.

For all the above-mentioned reasons, the Fundación de Ciencias de la Salud and the Spanish National Network Center for Research in Respiratory Diseases (CIBERES) organized a meeting, about COPD in Spain, bringing together experts from very different areas, as well as patients and their associations. We aimed to discuss, not only the clinical manifestation or the treatment of the disease, but mainly the impact in patients' daily life, in their caregivers, and in other related areas such as: the economy, the non-specialized press, and the health-care system organization.

All participants received a series of questions about COPD, which the coordinators felt needed an answer based on evidence, otherwise also on opinion. Each one of the speakers presented one of the questions, providing the information that allowed, after a discussion among all the members of the panel, to reach a response agreed upon by all.

As a disclaimer, all panel members participated, in their personal capacity, and the opinions they expressed do not necessarily represent those of their working groups or institutions.

This document is not intended to provide recommendations or therapeutic guidelines, but simply to help to establish a debate, and present an abridged collection of approaches and opinions of participants.

The meeting took place in Barcelona on October 31st, 2018, and this document tries to summarize the main issues discussed, the documentation provided on them and the conclusions that were agreed upon by the group. The final document has been approved by all participants, and it represents the group's opinion.

MATERIAL AND METHODS

Questions were chosen by the coordinators and agreed upon by all speakers. They were classified in three main groups of issues: the situation of the problem in Spain; its social and economic dimension; and the possibilities of effective improvement.

The document, edited in a first draft, was sent to all co-authors for their corrections and amendments. The final document has been reviewed and approved by all authors.

Next, we will review the questions posed, the arguments provided, and the conclusion reached by topic.

Question 1. What is the dimension of the COPD problem in Spain?

Text:

COPD is an important cause of morbidity and mortality in Spain, with a high health, economic and social impact. It is now widely recognized that COPD is a heterogeneous and complex syndrome, with pulmonary and extrapulmonary involvement [1]. In usual clinical practice, the diagnosis of COPD is based on the evaluation of exposure to tobacco smoke or other harmful fumes and gases, the presence of persistent res-

piratory symptoms (exertional dyspnea, cough with/without expectoration) and the identification of a persistent airflow limitation, documented by spirometry after a bronchodilator test [1, 2].

While direct or indirect exposure to tobacco smoke is considered the primary, causal COPD risk factor, other environmental exposures (biomass, marijuana and other smoked or vaped substances, air pollution, occupational exposures, and else) may contribute to its development, as well as individual host factors (gender, genetic abnormalities, abnormal lung development, accelerated lung aging, or neonatal respiratory infections) may predispose to it [1, 2].

COPD screening should be considered in any person over the age of 50 with dyspnea and/or cough as well as exposure to risk factors, tobacco smoking being the most relevant [3]. The EPISCAN study, carried out in 2007, reported a prevalence of 10.2% of COPD in the general Spanish population 40 to 80 years old, with great variability among the participating centers [4]. Other studies such as PLATINO estimated even higher prevalence, 14.3%, in Latin American capitals over 40 years of age [5, 6]. Previously, IBERPOC estimated that in Spain 1,228,000 people between 40 and 69 years old suffered from COPD [7].

Variations in COPD prevalence are largely a reflection of cumulative exposure to tobacco smoke. During the last decade, health policies have changed, with the entry into force of the Anti-smoking Law 28/2005 of 2006 and the subsequent amendment of 2011 by Law 42/2010. On the one hand, it is sensible to think that these health interventions of primary prevention could contribute to a decrease in the prevalence of COPD, since tobacco in Spain continues being the main cause of COPD. On the other hand, since the first EPISCAN study, forms of smokeless tobacco such as electronic cigarettes have appeared, and it will be of interest to assess the impact that this type of device has had on the smoking of the population and on the development of COPD and other respiratory conditions.

Conclusion:

The prevalence of COPD in Spain is high and is estimated to affect more than 10% of the adult population. The geographical variation is wide, and the most important and consistent risk factor is tobacco smoke.

Question 2. Is there a significant COPD underdiagnosis? Of what magnitude? For what reasons?

Text:

It is well established that tobacco smoking is the first cause and the most important risk factor for developing COPD in Spain. In patients who continue smoking, lung function decreases more rapidly than in those who quit. At any rate, the frequency of tobacco use remains high, and a high proportion of patients with COPD (close to 40%) continue smoking despite suffering symptoms of the condition [3].

According to the National Health Survey 2017 of the Ministry of Health, Consumption and Social Welfare of Spain, in 2017, the prevalence of smokers fell to 22% of the population, the lowest figure in the last 30 years. The report also presented important differences between men and women: 25.6% of men smoked daily, compared to 18.8% of women. The previous figure, from the 2011-12 survey, was close to 24%. However, this decrease is taking place at a slower pace in women than in men.

During this meeting, the results of EDADES, the Survey on Alcohol and Drugs in Spain, were released. The number of minors who had smoked in the last year increased from 20.6% in 2015 to 25.4% in 2017, and globally there was a notable increase in smoking to reach a worrying 34% of adults in 2018, which should be monitored.

More resources should be devoted to controlling tobacco smoking in the population and, above all, in patients with COPD, which could be carried out at different levels: state regulations, educational interventions, cutting smoking in current smokers ... It is well known that a simple, brief advice from a health-care professional increases the likelihood of quitting smoking. However, the overall success rate of smoking cessation is low. Consequently, there is an urgent need to demonstrate the efficacy of all interventional strategies in tobacco use, including a report on lung age. It is essential to underline the need to treat tobacco addiction (ICD10 F17 disease) as a chronic, relapsing disorder. Health professionals have an obligation to emphasize to our political representatives the need to promote research into smoking cessation.

Despite its high prevalence rates, COPD remains a disease with high rates of under-diagnosis, with percentages in Spain of 78% in 1997 and 73% in 2007. This fact leads to diagnoses in advanced stages, when there is a greater risk of exacerbations and mortality [8]. It is estimated that more than 1,595,000 Spaniards do not know they suffer from the disease and, therefore, do not receive any treatment for their COPD. The reasons for this are multiple and complex. The main one is the low use of spirometry in the general population and in the "at risk" population. There is an association between not having a diagnosis of COPD and living in rural areas, being female, having a younger age, low socioeconomic level, and absence of a previous history of smoking [9].

The global estimates in 2010 indicated that COPD was already considered the third global cause of mortality [10, 11], so an early diagnosis is of vital importance.

In 2017, a new epidemiological study was planned to update the prevalence and determinants of COPD in Spain, with representation from all 17 Autonomous Communities (CCAA). The aim would be to extend the assessment beyond spirometry, contemplating other dimensions with questionnaires of respiratory and non-respiratory symptoms, a broader functional evaluation and, in some cases, biological tests such as inflammatory markers, and imaging with low-radiation computed tomography[12].

Conclusion:

The underdiagnosis of COPD is a generalized and universal fact. In Spain it is estimated that it exceeds 70% of cases and the reasons most frequently related to under-diagnosis are limited use of spirometry in the population at-risk, residence in rural areas, female gender, having a low socioeconomic level, and absence of a previous history of smoking.

Question 3. How to address the implementation of spirometry in Primary Care?

Text:

Spirometry is a diagnostic tool that should be widely performed in Primary Care, since it is there where patients with respiratory diseases, such as COPD and asthma, are most frequently detected: They will benefit from an early diagnosis that will allow both preventive and therapeutic measures to be taken to avoid their progression [13].

To make this possible, it is essential to train both the medical and nursing staff who should perform the test. This training should be regulated and include all the following [14-17]:

- Basic knowledge of pulmonary physiology.
- Indications and contraindications of the test.
- Knowledge of the measures necessary to achieve correct maneuvers.
- Recognize technical errors and know how to avoid them.
- Evaluation of the curves made, and selection of the most suitable according to acceptability and reproducibility criteria.
- Knowledge to interpret spirometric patterns.
- Ability to evaluate the patient's physical or intellectual circumstances that modify the technical requirements of the maneuver, such as patients in wheelchairs, mental problems, etc.

This technique should be known by all nursing staff and must be integrated with the rest of the techniques performed daily, to minimize waiting times. It would be advisable to avoid delays between the prescription and its performance, overall one week or shorter.

Training, in most countries, is carried out by means of accredited courses and workshops [18-20], lasting between 5 and 12 hours, which enable this technique to be carried out adequately in the health center, where most of the time only forced spirometries are carried out with a computerized spirometer. There are international [21] and national initiatives for the accreditation of "spirometrists", such as the "Spirometry Driving License" of the European Respiratory Society, [22] or the Training Course in Spirometry of the Spanish Society of Family and Community Medicine, [23] and the Federation of Associations of Community Nursing and Primary Care (FAECAP). This training must be completed with adequate recycling and maintenance of skills, through regular courses or workshops [18, 24].

Despite certain articles [25-27] of national scope, where an enormous variability between different autonomous communities is identified, and the low adaptation to the quality criteria established by the national regulations on spirometries, there is a clear example that Primary Care spirometry is possible, which is the Balearics Program of Spirometry in Primary Care. There, after a comprehensive training in spirometry, a significant improvement has been achieved since its implementation in both process and result aspects, with an increase in the number of spirometries in all centers, in the proportion of patients diagnosed with asthma and COPD with spirometry, and in the proportion of quality spirometries.

Conclusion:

Spirometry is a technique that should be performed in Primary Care by properly trained nurses, through courses currently available in both national and international scientific societies. There is a great interregional variability in the performance of spirometries in Primary Care in Spain, being the Balearics Program one of those that has accredited and demonstrated better results.

Question 4.- What is the burden of work-related and personal disability due to COPD?

Text:

There is no available macroeconomic data in Spain on the distribution of sick-leaves due to COPD [28]. In a recent report, pooling data on temporary work disability in Catalonia between 2010-15, the main cause was respiratory conditions, which caused 21% of them, excluding those due to infections or tumors [29].

COPD costs can be divided into direct costs (drugs, tests, hospital admissions, consultations, etc.) and indirect costs (permanent disability, sick leave, career-related, etc.), the latter being always more difficult to measure. It is estimated that 60% of the expenses generated by COPD are attributable to indirect costs [30].

Another relevant point for estimating work-related costs of COPD is the percentage of COPD patients of working age. In studies based on surveys, this percentage ranges from 23 to 36%, increasing in prevalence studies to 45% (30-32).[30-32]

In two Spanish studies, between 8 and 13 % of patients with COPD in active employment had had sick leave in the last year [32, 33]. In another study, published in 2018, on 3,627,107 episodes and 237,219,230 days of temporary incapacity in Catalonia between 2007 and 2016, 3% were considered to be due to tobacco, of which 66% of the episodes and 23% of the days on sick-leave were attributable to respiratory causes [29].

Extrapolating the previous data to the national set, we can calculate that in Spain there are about 3,000,000 patients with COPD, and among them there would be between 100,000 and 150,000 lost work days per year.

As for permanent disability, it has been estimated that 5 to 10% of all permanent disabilities in Spain are due to COPD [32-34]. The cost per patient of permanent, early retirement has been estimated at 5,645 euros per patient [35, 36]. To this amount, the cost of the caregiver should be added, plus nursing homes and those due to COPD comorbidities.

The calculation of Disability-Adjusted Life Years (DALY`s) is a way of quantifying the burden of an illness, by taking into account years of life lost plus years of life lived with disability. A DALY can be considered as a health-weighed lost year of life. Data from Spain corresponding to 2016 show that COPD caused a total of 654.4 x 100,000 (610.9-705.7) DALYs, being the 7th cause in the overall ranking of causes of DALYs, that is contributing to 2.8% of the total DALYs. The number of DALYs due to COPD is highly variable, depending on age and sex, increasing more than 10 times in men over 80 years up to values of 8,274 x 100,000 (7,417-9,259). In this age group, COPD represents the 3rd position in the overall ranking of DALYs, just behind ischemic heart and Alzheimer's disease.

Conclusion:

In Spain, COPD generates between 5% and 10% of all permanent sick-leaves. Globally, COPD is attributed with 650 DALYs per 100,000 inhabitants, although in men over 80 years this rate increases up to to 8,274 DALYs per 100,000.

Question 5.- How much does COPD costs to society? How does Spain compare with countries of similar level of development in this aspect?

Text:

It has been already mentioned, 10.2% of individuals aged 40 to 80 years old in Spain have COPD, [4] and this trend is expected to increase, due to population ageing. In a large study carried out more than a decade ago in the USA, the average direct annual cost of COPD was calculated at 1,876 USD per patient, although this cost depended on the severity of the patient (from 1,484 to 2,911 USD). Of this expenditure, 43.8% corresponded to hospital expenditures, 40.8% to drugs, and 15.4% was due to diagnostic tests and medical visits [37].

A very recent study in Extremadura, calculated an average annual expenditure per patient with COPD of 3,077 Euros, with a distribution that attributes 43.8% to direct health expenditure (1,645 Euros), 38.3% (1,440 Euros) to direct non-health expenditure (non-health centers, caregivers, etc.) and 17.9% (672 Euros) to productivity losses[38].

It is worth noting that, despite the increase in drug prices for COPD, costs have remained very stable, between 1,876 USD and 1,645 Euros/patient/year in both studies almost 15 years apart. It is likely that the higher cost of drugs is been offset by a decrease in hospital costs, due to a greater effectiveness of various treatments for COPD. If we use the most recent study, we can calculate an overall COPD cost of 36.2 million Euros for Extremadura in 2015, which extrapolated to the remaining Spanish population adds up to a COPD global cost in Spain of 1,547 million Euros in 2015.

COPD costs in Spain are significantly lower than those observed in surrounding countries, due to the lower costs associated with health care in our country. Thus, in Germany, the average annual cost of a patient with COPD is 7,263 euros [39], and in Greece it has been calculated at 4,730 euros [40]. Of course, in North American countries the cost is significantly higher: in Canada, where it reaches an average of 8,600 Canadian dollars [41]. Again, these costs do not reflect differences in prevalence, severity or prognosis, but rather the lowest manpower cost in Spain.

Given these figures, we must ask ourselves: what is being done to prevent COPD? Likely, the answer is that there is no direct investment in preventing the COPD epidemic. The best option is prevention of smoking, and restrictive legislative measures have been a great step forward, which should translate into a reduction in the costs of COPD in the decades to come. Other alternatives are the prevention of exacerbations, and reductions in the progression of the disease with appropriate treatment, physical activity, and vaccination, among other interventions.

Conclusion:

Estimates based on data from Extremadura (Spain), conclude that approximately € 3,000 per patient is the average annual cost of a patient with COPD in Spain. This adds up to an estimate of 1,547 million Euros cost in 2015 in Spain.

Question 6.- What are the main preventive measures for COPD? What is their effectiveness?

Text:

COPD is caused primarily by inhalation of tobacco smoke and, to a much lesser extent, by inhalation of biomass smoke, a more frequent cause in developing countries. Tobacco use is particularly relevant in respiratory medicine, as it is also the leading cause of lung cancer. Tobacco use is a predisposing factor for respiratory infections including pneumococcal pneumonia, influenza and tuberculosis. People with the least education, those with the least purchasing power, those between the ages of 18 and 24, and those working in construction are the most likely smokers. There are currently more than one billion smokers in the world. Active and passive smoking is responsible for more than 6.3 million deaths annually, which represents 6.3% of the total burden of disease. The WHO goals are focused on reducing the demand and sale of tobacco in the world through educational strategies, policies and legislation [42].

Tobacco smoke contains an aerosol of particles including water, nicotine and thousands of chemical substances that are harmful to the human organism, by absorption of toxins and

by local toxicity in the lungs through chemical oxidants. Tobacco use is the cause of 80% of COPD, either emphysema or chronic bronchitis. The mechanisms causing COPD by tobacco are complex and include inflammation and direct lung damage by oxidative substances, increased elastase activity (proteins that act against elastins and connective tissue), and decreased antiprotease activity.

The most effective preventive measure against COPD is tobacco control and cessation. Of the total number of smokers, 70% acknowledge their intention to quit smoking, and approximately half try at least once a year. Spontaneously and individually, only 1% achieve effective quitting. With simple medical advice success reaches 3%. Minimum intervention programmes are effective in 5-10% of smokers, while more intensive treatments can be successful in 25-30%. Intensive treatments are not easy to implement, due to limited resources, although existing regulations recommend that all smokers attempting to quit smoking should have access to anti-tobacco drugs. The drugs approved to treat tobacco use are nicotine, bupropion and varenicline. In a few studies, all of these drugs have been shown to double cessation of tobacco use compared to placebo. Concomitant administration of nicotine (long- and short-duration) with bupropion or varenicline increases the effectiveness of the treatment.

The benefits of quitting smoking are evident at any age and include: decreased risk of cancer, decreased risk of acute myocardial infarction, decreased loss of lung function, and in pregnant women, decreased likelihood of giving birth to low birth weight infants. In general, patients who quit smoking may gain 10 kilos of weight, and this may be a reason for some patients not to stop smoking [43, 44].

Conclusion:

The most effective preventive intervention against COPD is smoking cessation. Although 70% of smokers want to quit, and half try it once a year, only 1% quit successfully without any help; 3% achieve this only with simple medical advice, 5-10% with minimum interventions, and 25-30% after intensive treatments that include anti-smoking drugs.

Question 7.- How do aging and chronic diseases affect the lives of patients with COPD?

Text:

Life expectancy in most countries has increased in recent years, although ageing is associated with an increase in chronic diseases and disability. We are witnessing what Fries called the Theory of Compression, as early as 1980 [45]. We live longer, but disability and aging are compressed in the last years of life. It is tantamount to saying that we age later and renders obsolete the classic definition of "old", applicable to anyone over 60 or 65 years of age.

Cohort studies carried out in nonagenarians, 10 years after their inclusion in the study, show that the nonagenarians of the most recent cohorts had longer life expectancy, less disability, less cognitive deterioration, and even less brain atrophy measured by magnetic resonance (physiologically the brain size decreases with age)[46]. Data from the "Global Burden of Disease Study" show that between 1990 and 2013, years lived without disability had increased in a manner similar to life expectancy [47].

When exploring old age and COPD, the first problem that arises is that in elderly patient's COPD is more difficult to diagnose, given the presence of comorbidities that can mimic similar symptoms (e.g. heart failure), or limit exercise capacity (e.g. peripheral vascular disease). In addition, patients sometimes mistakenly attribute dyspnea to a natural process associated with aging. Spirometric confirmation is also more difficult in the elderly, since 25% of them cannot perform quality spirometry, and the time required for its performance is longer. In this sense, devices that use the FEV1/FEV6 ratio may be useful, since the greatest difficulty in the elderly population is completing forced exhalation [48, 49].

Elderly people hospitalized for a COPD exacerbation have less spirometric severity, but more symptoms and more comorbidities [50]. Another important issue is the difficulty in correctly using inhalation devices, due to the impossibility of "doing the clamp", dyspraxia or insufficient inspiratory capacity. It is therefore essential to check its correct use, in many cases with the help of the caregiver. And in doubt, it is recommended to use devices that assure that the inhalation has been correct.

In the elderly, frailty is frequent, meant as a diminished functional reserve, which in case of presenting a complication can lead to disability. It is estimated that a hospitalization due to COPD causes a loss of 5% of the strength of the quadriceps, and that the time required to recover the ability to walk is greater than in young people [51]. Finally, the presence of several comorbidities that interact with each other is frequent in elderly persons, making it virtually impossible to identify a main condition, so that in many cases the use of the term multimorbidity is preferable to that of comorbidity.

Conclusion:

Ageing and its related accumulation of diseases, makes diagnostic confirmation of COPD more difficult, because symptoms may be attributable to other diseases. Correct performance of spirometry tests is more difficult in this population.

Question 8.- How is a day in the life of a patient with advanced COPD? The vision of a patient.

Text:

Life with COPD is complicated. With discipline, will, and external help you can aim to having a life like that of a healthy person, but not the same. Everything is much slower, and therefore everything must be very programmed. Portable oxygen therapy allows to make social life outside the home, but slowly and programmatically. And at the end of the day, a great deal of tiredness accumulates, and you must retire soon.

The main limitation is mobility. A lot of help is needed for many things, especially boarding vehicles, getting into elevators, etc. All movements must be programmed and knowing in advance the accessibility of the places you are going to visit. Another important limitation is the provision of oxygen, as the backpacks last 4 hours, and then you must go back home to recharge. We often stop going to events because of the difficulty in overcoming unforeseen events, but by planning we can do almost anything.

I am asked if the COPD is a stigmatized disease. Personally, I do not feel that way, but other patients may feel stigmatized. I have been with this disease for a long time, and I consider that the stigma disappears more and more, and that it has been diminishing in the last years. One aspect to be commented from the perspective of a patient is the frequency with which COPD patients feel misunderstood and try to "justify" their situation. Friends and relatives tend to think that we are comfortable, and that we do not do certain things because we do not want to.

Conclusion:

The life of a COPD patient with advanced disease is limited by the lack of mobility, the need for portable oxygen therapy, and the slowing down of all activities. Activities of daily living must be highly programmed, unforeseen events are mishandled, and the patient often blames him/herself, and needs to justify.

Question 9.- How does COPD impact the affective, psychological, social, sexual and spiritual spheres of the patient? The psychologist's vision.

Text:

Breathlessness is one of the most frightening experiences of any human being. The suffering that accompanies not being able to breathe, or doing so with difficulty, blocks and stops any activity [52]. A headache, as long as it is not incapacitating, or a toothache, allow us to continue with certain activities, but lack of air does not. There is no need to point out the impact this has on people, at all levels. Several studies quantify the presence of anxiety and depression in COPD patients [53]. The consequences of COPD are felt beyond physical problems: it is a disease that, because of its main symptom, affects the whole person. The emotional impact is undeniable, and these emotions vary from day to day. Precisely, being able to manage emotions, not blocking them, can make the patient manage better or worse, their day to day.

The patient's loss of autonomy leads to a feeling of global dependence and denial. He/she rejects all sorts of activities, even the most intimate ones, such as affective or sexual activities. It accompanies the sensation of failure, discouragement, hopelessness and sometimes even loss of meaning in life. This is what we would call "demoralization syndrome", while the main difference with depression would be anhedonia; a patient with depression is unable to enjoy anything.

On the one hand, COPD patients tends to isolate themselves from the general world, from family, and even from himself. Sometimes they identify with the oxygen concentrator and forgets his philias and phobias. On the other hand, patients feel shame and guilt because they understand that certain unhealthy life habits, such as smoking, led them to this situation. Guilt is one of the most complex emotions to deal with, since it is related to "repair", something barely achievable in this situation.

All this, if not addressed from the beginning and as the disease progresses, inevitably means the loss of a sense of dignity as a person. Dignity, like demoralization and emotional distress (anxious-depressive pictures) configures one of the essential needs of the person: spirituality [54]. We understand spirituality as an intrapersonal dimension (sense of coherence), interpersonal (relationships with others and feeling of peace) and transpersonal (legacy, hope). The person with COPD often identifies more with the idea of "sick" than with the real idea that it is "he/she himself/herself".

The care of emotions of any person with COPD is the main preservative of dignity and, therefore, of quality of life.

Conclusion:

Anxiety and depression are two common manifestations associated with COPD, conditioned by the loss of autonomy and dependence on many activities of daily living. The care of emotions, and their management, is the main way to preserve dignity and, therefore, quality of life.

Question 10.- How does the presence of a COPD patient impact the family? Vision of the non-professional caregiver.

Text:

The caregiver is a fundamental pillar for patients with COPD. We will distinguish between health professionals and informal caregivers such as friends, family, neighbors, which in most cases are those who will provide care at home. This role is often underestimated, both in the literature and in many of the documents that deal with the disease. We can see how those patients who have a caregiver have a better tolerance to exercise, fewer readmissions, and better adherence to treatments, than those who live alone [55, 56]. Sometimes the caregiver's vision, especially when dealing with a close relative, is to be caring for a fragile person. This worry with what the patient may suffer has negative consequences for the patient due to the anxiety and fear that this may cause, leading to overprotection of the patient, and making him or her more dependent. Hence the importance of the education that health professionals must provide, not only to the patient, but also to caregivers.

Dyspnea is the main symptom of any COPD patient. And together with fatigue, cough and altered sleep patterns, limits physical activity and activities of daily living [57]. Overall, 57% of patients who suffer from dyspnea in their severe or very severe stages have morning symptoms which will prevent

them from showering or dressing autonomously [58]. This affects family life to the point of having to change habits, to live together as a couple, or to stop sharing activities, forcing the patient and the family to implement strategies to minimize the consequences of these symptoms. In patients of working age, these limitations may imply a change or interruption of their professional activity, with the socioeconomic consequences that this entails.

The caregiver is often responsible for medication and symptom management, will provide assistance in activities of daily living, and will provide physical and emotional support to the patient. This increased workload will affect the patient's social and working life, and the caregiver may experience anxiety, worry, fear for the future, loss of autonomy and social life, and finally depression. These symptoms tend to increase as the disease progresses. In the final stages of COPD, the fear that the patient may die with suffering becomes a cause of greater emotional stress. Caregivers often complain that the information, emotional treatment or support they have at home is insufficient [59]. Yet they are forced to constantly adjust their role, with reconsideration of their needs.

But caring can also be positive and rewarding and teaching the caregiver how strong he or she can become is essential [60]. Hence the importance for health professionals to care for and accompany the caregiver during this journey, and later in the process of adjusting to the loss of care during the bereavement phase [61].

Conclusion:

COPD patients with caregivers have better exercise tolerance, fewer readmissions, and better adherence to treatments than those without caregivers. Caring for, teaching and supporting the caregiver on their endeavors is an essential responsibility of health-care workers

Question 11.- What is the role of nursing in COPD?

Text:

The role of nursing in COPD is fundamental in aspects such as health education, and for the implantation of healthy habits, with the aim to improving/maintaining the patient's quality of life [1, 23]. Education and support should also be aimed to family and caregivers.

Nursing is directly responsible, among others, of the following activities:

1.- Revise treatment to clarify doubts and avoid mistakes.

2.- Revise inhalation technique.

3.- Training in the handling of inhalers, inhalation chambers, rescue inhalers and nebulizers.

4.- Evaluate change of inhalers.

5.- Check the correct use of chronic home oxygen, both fixed and portable, in terms of use, hours, liters, mode.

6.- Resolve doubts about non-invasive mechanical ventilation (NIV).

7.- Review the cleanliness of materials (inhalers, chambers, nasal goggles, humidifiers...).

8.- Check food and water intake.

9.- Revise physical activity and respiratory rehabilitation.

10.- Teach energy saving techniques.

11.- Encourage self-care.

12.- Control vaccination schedule.

13.- Program strategies for smoking cessation.

14.- Teach how to recognize and react whenever a COPD exacerbation occurs.

15.- Help to program and maintain leisure time.

16.- Help in the programming of trips and vacations.

17.- Serve as a liaison with the Social Worker.

18.- Development of learning and reinforcement workshops for the patient´s caregivers.

19.- Support during the progression and worsening of the disease, and during the end of life.

Conclusion:

The role of nursing is essential in the care of COPD patients. There is a direct responsibility for patient and caregiver's health education, and in the psychosocial support for both.

Question 12.- Women and COPD. Does COPD choose gender or does gender choose COPD? Is COPD different in women?

Text:

COPD is characterized by a chronic, progressive and irreversible limitation to airflow associated with exposure to tobacco smoke and, to a lesser extent, to occupational and environmental inhalants or products derived from biomass combustion. In addition to exposure factors, there are other host-related factors, such as genetic susceptibility or abnormal lung development, that predispose individuals to develop the disease [62-64].

In Spain, data from the EPI-SCAN study concluded that COPD prevalence reached 10.2% (15.1% in males and 5.7% in females) [65] while, ten years later, preliminary results from EPI-SCAN II (unpublished) suggest that the prevalence of the disease rises, and its increase is more remarkable in females (9.5%) than in males (16.9%), with still a high rate of under-diagnosis.

In Spain, ageing of the population, more pronounced in women due to their greater longevity, and their massive incorporation into tobacco use around the 1970s, has led to an increase in respiratory diseases associated with smoking in women. The latest National Health Survey, published in 2017, indicates that while in men there is an annual decrease in smoking (18 percentage points since 1993), in women, there has been a phenomenon of maintenance with leveling off, However, with alarming trends among the youngest, where

girls already outnumber boys in tobacco use. In spite of this, COPD is still considered a disease that mainly affects men, which constitutes a diagnostic bias that contributes to the greater under-diagnosis in women in Spain [66, 67].

Female smokers are more susceptible than male to the harmful effects of tobacco, due to genetic, anatomical, and hormonal factors, and develop more severe and earlier-onset forms of COPD [68-70].

In published studies, women refer a greater degree of dyspnea than men for the same degree of airflow obstruction, and lower tobacco exposure [71, 72]. However, women present comparatively lower sputum production than men, which may be influenced by social factors [73]. Nutritional status, a fundamental clinical parameter to be evaluated in patients with COPD due to its potential as a prognostic predictor, seems to be altered more frequently in women [74, 75], who also present more COPD exacerbations than men [76, 77], although with lower rates of re-hospitalization and better survival[78].

Regarding comorbidities, or diseases that are associated with COPD throughout its progression and interfere with the health status and prognosis of these patients, their expression is also different by sex. Data from the ECLIPSE study Agusti,[79], indicate that cardiovascular diseases are less prevalent in women with COPD, while disorders of the affective sphere are more frequent than in men. The presence of anxiety and depression in COPD-affected women has an important impact on the disease, both because of its influence on symptom control and quality of life, and because of its relationship with prognosis, since it is associated with a greater risk of exacerbation, longer hospital stays, persistence of tobacco consumption, less physical activity, greater mortality and, possibly, less adherence to treatment [73]. Osteoporosis, with a prevalence close to 35%, also predominantly affects women, especially in post-menopause, and correlates with more severe forms of COPD and a low nutritional status [78].

In terms of treatment, published studies show that women tend to stop smoking less frequently, and that their success rate in long-term smoking cessation is lower than that of men [80, 81]. Finally, in home oxygen therapy or respiratory rehabilitation, few studies have been designed to evaluate their efficacy according to sex, so the available information is scarce and even contradictory.

For all these reasons, COPD constitutes a growing health problem, especially in women. Priority should be given to improving clinical suspicion and clinical characterization, to optimize the therapeutic approach in female COPD patients.

Conclusion:

COPD is a growing health problem, especially in women. Priority should be given to improving clinical suspicion and clinical characterization to optimize the therapeutic approach in these patients.

Question 13. What does the media know and what does the specialized and non-specialized press publish on COPD? What does the "World COPD Day " represent?

There is a disproportion between the impact of COPD on public health and its presence in the general media. If we assess La Vanguardia, over a period of two years as a case study (October 2016-September 2018), we observe that COPD has been cited in 14 articles, in one of which it has appeared in the headline ("An Everest for patients with COPD", by Rosa M. Bosch, 6/4/2017). If we extend the sample to chronic bronchitis and emphysema, it has been cited in a total of 18 articles. Although it is the third cause of death in the world according to the WHO, it is not the third disease with more presence in La Vanguardia.

To understand the reasons of this discrepancy, it is instructive to look at the coverage of other diseases with the greatest mortality impact: ischemic heart disease (9.4 million deaths in 2016; cited in 131 articles; 28 headlines); stroke (5.8 million; 101; 18); cancers (9.6 million; 584; 198); Alzheimer's and other dementias (1.9; 122; 44); diabetes (1.6 million; 148; 17); diarrhoeal diseases (1.4 million; 33; 4); tuberculosis (1.3 million; 71; 8); AIDS (970,000; 201; 63); malaria (470,000; 51; 11) [82]. These data show that there is no direct linear relationship between the epidemiological impact of a disease in terms of mortality, and its presence in the media. Should we analyze those diseases not with the highest mortality, but the most disabling ones, such as depression or chronic back pain, a similar pattern emerges.

In order to understand the criteria on which a disease has more or less presence in the media, it is convenient to identify commonalities with those conditions most frequently reported (cancer, AIDS) and differences with those that are less covered (COPD, diarrheal diseases). This analysis reveals different variables with different relative weights. The two variables that have more weight are, on the one hand, the appearance of novel and relevant medical information associated with the disease and, on the other hand, the fact that a disease is associated with well-known public people.

Cancer and AIDS are examples of diseases that meet both requirements. At the other extreme, diarrheal diseases and COPD do not meet either of the two for the Spanish media.

All of the above diseases have a World Day on the calendar, indicating that the variability in information coverage between them does not depend on having a World Day or not.

An additional handicap of COPD is in its name, which is unfamiliar to large sections of the population. A similar handicap has affected in recent decades stroke, which displaced terms that are better known among the population, such as embolism or apoplexy. In the same way that stroke has become an everyday word, it is to be hoped that COPD will also do so in the future.

Conclusion:

There is no direct relationship between the frequency of a disease as a cause of death, and its media coverage. The diseases most frequently cited in media are those in which either the most "novel" medical information is

produced, or in which celebrities are involved. Having a World Day is not a factor of relevance.

Question 14.- What are the current strategies for COPD? What are the alternative solutions to improve their quality and effectiveness?

Text:

The National Strategy Against COPD has had, so far, a positive impact. However, there is a lack of resources (human and economic), a lack of quality spirometries and proactive diagnosis, deficient computer systems, great variability in care, low adherence to Clinical Practice Guidelines, deficient training in self-care, deficient care coordination, and far too high rates of readmissions.

In relation to COPD, the National Health System (SNS) in Spain confronts an increase in chronicity, a greater demand for care, a growth in technological complexity and an increase in dependence, and the need for social health care. These are all important elements for a "perfect storm". To them it must be added the deep economic and social crisis, and an unsustainable model of health and social protection. Should there be no reforms a crisis of the system is envisaged.

The most relevant factor is demographic ageing. The population aged 65 years and older would account for 25.2% of the total in 2033 [83]. The coincidence in time of a formidable increase in the population to be treated, aged and multi-morbid, consuming enormous health resources, in a context of health budgets with little annual variation and very tight (downwards) to changes of GDP is "the perfect storm" [84]. There is no ongoing reform of the NHS, to achieve long-term sustainability and to avoid future recessions [85].

To overcome this storm, *"we must be ready to reorganize the health system with new policies, plans, and programs, and be willing to convince decision-makers that only by acting on three pillars - patient-centered care, hospital efficiency, and carrying out interventions in the optimal (home) environment - can we avoid disaster*" [84].

The Spanish NHS needs strategic management of future crises, identifying trends and anticipating solutions before it is too late [86]. If the urgent displaces the important, it prevents us from facing any long-term challenges. It is the "curse of short-termism" that takes away our time for reflection, without the capacity to adapt and anticipate. Reforms and changes are delayed "sine die" [87].

We need quality information on the impacts of current decisions and their alternatives, with appropriate measurement instruments and a multi-system thinking approach [88]. There are no simple solutions to complex problems. We obtain an enormous amount of data which, if well analyzed and shared, should enable the implementation of public policies backed by objective data [89]. We should avoid unfounded or improvised policies that are never evaluated. Some alternatives might be:

- A more efficient, flexible, modern, professional and independent organizational structure.
- A strong political and institutional support, (i.e.: clear, public and transparent), with a guaranteed budget.
- Involvement of patients in decision-making (information and education) and in increasing home treatment.
- Improve coordination with the Autonomous Regions.
- Integrated and compatible clinical history.
- Comprehensive care process (PAI) with exacerbated COPD, avoiding re-entries [90].
- Respiratory rehabilitation, palliative care, control and treatment.
- Effectiveness against smoking.
- Innovate, go to a results-based model (ICHOM). Behavioral economics [91], digitization, and big data.

Conclusion:

The current conditions in the approach to COPD of the National Health System favor "the perfect storm". The ageing of the population and the increase of the necessary resources require a serene and long-term planning that seems incompatible with the management of "the urgent".

Question 15. COPD beyond tobacco.

Text:

COPD has, traditionally, been considered as a self-inflicted disease due to tobacco use [92]. Thus, in some genetically susceptible individuals, inhalation of tobacco smoke produces an excessive inflammatory response [93] which, in turn, causes accelerated loss of lung function with age [92]. Subsequently, it was recognized that inhalation of other particles and gases, such as those derived from the combustion of biomass for domestic use, was also a significant COPD risk factor, especially in developing countries [94, 95]. And, even more recently, it has been proven that alterations in pulmonary development, during pregnancy and after childbirth, due to genetic and/or environmental causes, are also an important risk factor for COPD [96]. In fact, approximately half of patients diagnosed with COPD in clinical practice, often in their fifth or sixth decade of life, already had evidence of poor lung development by the age of 30 [97]. It has also been shown that poor lung development is associated with poor development of other organs (cardiovascular, metabolic) resulting in a higher prevalence and incidence of co-morbidities at early ages, and higher mortality [98]. The observation that COPD goes beyond tobacco opens new opportunities for its prevention and treatment [99].

Conclusion:

Tobacco use remains the main risk factor of COPD. However, it is not the only one. Inhalation of gases other than those produced by tobacco is also a cause of COPD. In addition, very recent research indicates that poor lung development before or after childbirth may also contribute to the pathogenesis of COPD (and other chronic diseases) in adulthood, opening new opportunities to

implement much earlier prophylactic and/or therapeutic measures.

Question 16.- What do Clinical Practice Guidelines contribute? How should the Guidelines of the future be?

Text:

Clinical practice guidelines (CPGs) aim to improve the quality of health care and reduce variability in the treatment of patients. CPGs make treatment recommendations based on available evidence and, when evidence is not available, based on expert opinion. In recent years GPCs have evolved towards a greater recognition of the imperative need for a systematic approach to evidence and a very rigorous manufacturing process to ensure that only accurate and appropriate recommendations are issued. The use of methodologies such as GRADE (Grading of Recommendations Assessment, Development and Evaluation) allows for the elaboration of recommendations that are robust and as free of bias as possible [100]. However, the use of this methodology implies a very high cost in time and money and limits the application of the guide to a series of previously defined assumptions in the form of PICO questions (patients, intervention, comparison, outcomes). This fact, together with the difficult interpretation by clinicians of the results of the GRADE system, has implied that various scientific societies have tried to find ways to improve and/or simplify the elaboration of GPCs without losing reliability. For example, the American College of Chest Physicians has initiated what they call a hybrid process, that includes recommendations based on evidence according to the GRADE system; and when the evidence is insufficient, they combine it with a Delphi process to reach a consensus that results in reliable positioning [101]. To this end, they have developed a structured process that includes a systematic review of the literature and very strict rules on expert participation and voting [101].

The American Thoracic Society (ATS) is developing the CORE (Convergence of Opinion on Recommendations and Evidence) process, which aims to discriminate at the beginning of the development of the GPC those recommendations that should be developed through a systematic review of the literature and those that can be based on expert opinion. The CORE is a type of modified Delphi, which in a study showed that it offers very similar results to the GRADE process in many recommendations, which would in many cases allow recommendations to be formulated with great savings in time and resources [102].

The European Respiratory Society (ERS) has initiated a mixed process in the development of GPCs that includes the formulation of PICO questions, and a systematic review with recommendations according to the GRADE system, but together with non-PICO questions in aspects where there is no evidence and that will generate recommendations based always on the EtD (Evidence to Decision) process [103] to explain in a clear and transparent way, what type of information has been used to establish the recommendation [104]. In any case, the challenge for future GPCs is to develop evidence-based recommendations, free from bias and useful to the clinician [105].

In Spain there is the Spanish COPD Guide (Gesepoc) led by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR). It is conducted in collaboration with all the scientific societies involved in the care of COPD patients, plus patient associations. Its first edition was published in 2012, and its latest revision in 2017 [106]. It is a GPC that uses the GRADE system of evidence evaluation, and has had a progressive implementation, so that in 2016, 46% of the clinical charts of patients with COPD audited in Spain included the classification according to the Gesepoc guide.

Conclusion:

Clinical Practice Guidelines offer a series of recommendations based on scientific evidence. CPGs are not without methodological problems and difficulties, but compliance improves clinical outcomes and patients' quality of life.

Question 17.- What is the CIBERES (Centro de Investigación Biomédica en Red en Enfermedades Respiratorias)? What has been the contribution of CIBERES to the management of COPD in Spain?

Text:

A few years ago, the Spanish Government decided to create specific research institutes and created the CNIC (National Centre for Cardiological Research) or the CNIO (National Centre for Oncological Research) on the grounds of the "Carlos III Institute". Each had a separate building, that was filled with researchers, and hired star directors with the aim of promoting research excellence in oncology and cardiology, two important pillars of a society's health.

Over time, maintaining the building and that structure has a fixed cost, which limits the return on investment. Some twelve years ago, other models of research centers were chosen, which are the CIBER (Centers for Biomedical Research Networks). In these CIBERs there are no buildings (networked centers), and what they do is to put in communication the existing teams and groups of excellence of each of the areas of knowledge. They are provided with a non-physical structure and are assigned a budget to manage it for the same purpose they had for the CNIC or the CNIO.

What do we gain from this? We gain that we no longer have permanent staff researching in a building, but we have the best of the country, working together in each of their specific areas, working cooperatively and avoiding the cost associated with the structure. Each Euro invested is much more efficient and generates much more knowledge. Another advantage is that the structure is not fixed and permanent, so that the groups that make up the CIBER do not have the right to remain indefinitely. After yearly evaluations, the "worse" of those are excluded, and other groups can apply and be included.

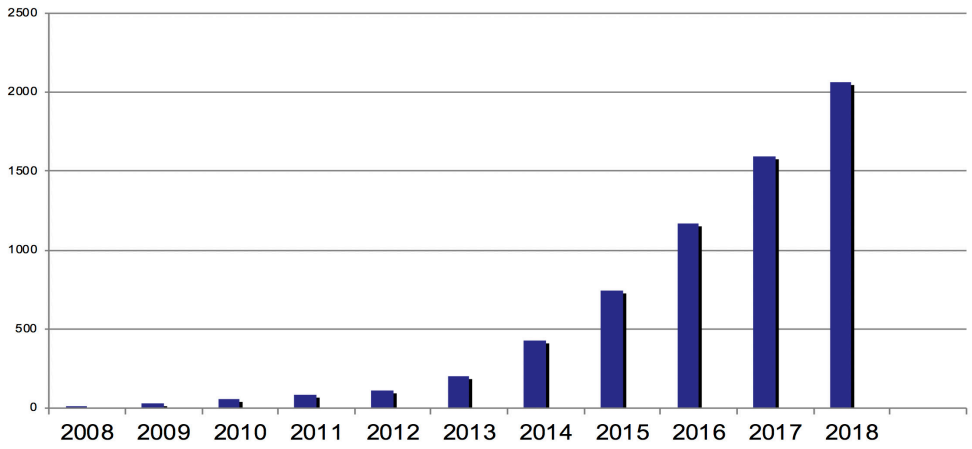

Figure 1 Progress of the overall scientific production of CIBERES followed through PubMed.

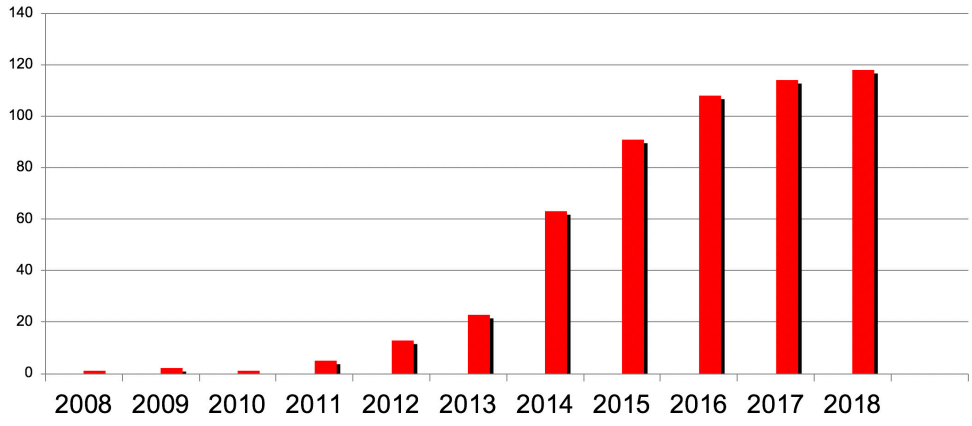

Figure 2 Progress of the scientific production in COPD, of CIBERES (number of publications indexed per year)

At CIBERES there are, nowadays, 34 research groups with different areas of interest in respiratory diseases. They represent the excellence of research in respiratory medicine in our country. That network has a scientific director, a management support structure, a management committee, and some internal and external scientific advisory committees, along with a minimal management structure that is physically in the Carlos III Institute in Madrid.

An annual budget of around 2.7 million Euros is received, and that money is distributed among groups that make up CIBERES, not equally, but according to the annual evaluation of each of the groups.

To evaluate the scientific contribution of CIBERES since 2008, we have carried out a search in PUBMED according to the following criteria: CIBERES (Affiliation) + Spain (Affiliation) + Year of Publication +/- COPD OR EPOC. With these criteria, we offer the evolution, in number of global publications and particularly referring to COPD produced by the network. The graphs (figures 1 and 2) are worth more than a thousand words and demonstrate the spectacular the impact of the

money invested in this research group in top-quality scientific production. We have not included the formative impact on new researchers, nor do we have any record of the impact all this has had on improving people's quality of life, but we do not doubt this relationship.

Conclusion:

CIBERES is a state organization for research in respiratory medicine. It brings together 34 multidisciplinary research groups. CIBERES, with 10 years in operation to date, has contributed to a better knowledge and management of COPD, with an extraordinary scientific production, and the training of countless Spanish researchers in this field.

Question 18.- What is the current paradigm of COPD? Could we speculate on the future of COPD for the year 2050?

Text:

Along the XXth Century, COPD was a disease associated with the triad of man, smoker, and older than 65 years. The current paradigm is changing and is that of a chronic disease associated with aging and smoking, requiring comprehensive treatment by specialists in Pneumology, but also Nursing, Primary Care and Internal Medicine. COPD is becoming feminized, and in the United States more women than men die with this disease. In Spain, it is estimated that in 2017 more than 28,000 people died with COPD, that is 17,300 men and 11,400 women. In addition, COPD is detected earlier, and patients live longer, so that the age of diagnosis, which before was usually between 65 and 69 years, now has a much wider range [11]. In the medium-term future, say in 2050, the burden of COPD could be reduced by reducing environmental pollution and controlling smoking (106). Tobacco use rates remain high in many developing countries and some developed countries, and indoor and outdoor pollution and occupational exposures are still serious problems in many countries. But the greatest current determinant of COPD is age. As life expectancy increases, and the ageing population increases, the burden of COPD can be expected to increase.

It is likely that promoting the development of better medical care, using newer and more effective drugs for COPD, and their increased adherence, will reduce disease-related mortality; thus, new cases of COPD will exceed the number of deaths caused by it, resulting in an increased burden of COPD.

Finally, it should be noted that the prevalence of COPD or airflow obstruction is more frequent in areas with a high prevalence of cigarette use. However, although it may seem a population paradox, COPD mortality is more closely related to the prevalence of low forced vital capacity (FVC) which, in turn, is more associated with poverty than with smoking [107, 108]. In 2050 there will be more people dying with COPD than from COPD; but since 2015, it is the third cause of death in the world, and the fourth in Spain.

Conclusion:

The current paradigm of COPD as a disease involving smokers, men, and those older than 65 years of age is changing rapidly. In the United States, more women than men die with COPD. The situation in 2050 is difficult to predict and will depend not only on factors such as trends in smoking, but also on changes in poverty and longevity.

Question 19.- What are the main objectives of patient associations? What should they change?

Text:

The WHO in 2008 wrote a report which showed that patient participation in their own processes can improve health outcomes, patient satisfaction, and even be economically beneficial [109]. In order to achieve these objectives, patients must join forces and associate. Patient Associations can play a fundamental role, being an important intersection between Public Health, health systems, health administrations, professionals, and society.

From a critical point of view, there are more than 6,000 patient associations in Spain; probably there are too many. They have very different levels of organization, development and action, and although there is a progressive improvement, it can be said that, in general, there is a lack of training, structure and leadership. There are, however, some well-structured and consolidated associations and federations.

Patient Associations can play a fundamental role, being a relevant intersection between Public Health, health systems, health administrations, professionals and society.

With a surge of patient associations [110, 111], the health system appears as a complex entity, with national, regional and local levels and with communication problems in all of them. There are problems of access to innovation, and inequalities in access to benefits, especially new therapies.

In our opinion, the main weaknesses of patient associations in Spain are:

- Scarce number of associates. Only 3% of patients belong to an association.
- Scarce economic resources. Subsidies are very scarce, and it is difficult to find resources from other sources.
- Physical limitations caused mainly by the disease or the recovery process of the people involved in its operation.
- Limitations of administrative knowledge. It is almost impossible to have associates, with time and useful professions, to deal with all administrative, legal and management issues, often complex and requiring significant dedication and qualification.

In Spain, FENAER (Federación Española de Asociaciones de Pacientes Alérgicos y con Enfermedades Respiratorias) [112] tries to "be the voice of patients" with allergies, asthma, COPD and other risk factors, and participates actively in decisions affecting health.

Conclusion:

Patient associations in Spain are probably exces-

sive in number and deficient in number of associates, and need stronger structures, better funding and more knowledge of the health administration. Such changes would help them to exert the necessary impact that is expected from them.

Question 20.- What is necessary to prepare and change the future of COPD in Spain? The view of healthcare administrators.

Text:

The National Health System (SNS) plans in Spain establishes the objectives and programming of activities of the public health administration. One of the objectives of the Quality Plan of the SNS is to improve care for the most prevalent diseases with the highest care, family, social and economic burden, including COPD [113] among them. It was in this context that the National SNS COPD Strategy was developed, which was divided into six strategic lines of action, one of which was research [114]. The general objectives of this strategic line were to promote epidemiological, basic, clinical and translational research, in aspects of prevention and comprehensive COPD care. The specific objectives were to establish priority lines of research, to promote, through their inclusion in calls for research projects, priority interdisciplinary lines of research in COPD, to implement measures to promote the creation of accredited networks of research centers and groups of excellence in COPD, and to promote research in primary care on COPD care.

The autonomous communities in Spain have also developed health plans. For example, in Catalonia the 2016-2020 Health Plan has selected nine priority areas of prevalent chronic health problems, one of which is respiratory diseases [115]. In addition, the Health Plan has also prioritized research and innovation through the development of the Strategic Plan for Research and Innovation in Health [116]. The thematic priorities of this Strategic Research Plan are aligned with those established in the Catalan Health Plan, and respiratory diseases have been included as one of the preferred topics.

On the other hand, there is also private promotional research that is developing new products based on the discovery of new therapeutic targets [117]. In approaching the incorporation of pharmacological research, it is necessary to anticipate and plan for access to future innovation. In this sense, an axis of work of the public health administration has been the creation of a "radar" or "horizon scanning" system of pharmacological innovation, to anticipate and plan access to it in the public health system [115]. Furthermore, it is necessary to evaluate the pharmacological innovations that are marketed in order to determine the added therapeutic value that they provide and to guarantee equity in access to these innovations in the field of public health, in accordance with the principles of effectiveness, safety, efficiency and sustainability of the public health system, as well as the conditions of use, access and provision.

Conclusion:

COPD is one of the main objectives of the national and regional health plans in Spain. The plans include several strategic lines, one of which is the promotion and stimulation of research. On the other hand, the public health administration also assesses the added therapeutic value of innovations, to ensure equitable access within the national health system.

Question 21.- What reflections from the ethics perspective do we propose?

Text:

COPD, as its name indicates, has chronicity as one of its main characteristics. The distinction between acute and chronic processes is as old as Western medicine itself. It is already found in the Hippocratic writings, those with which our medicine was born. On those writings, one of the main characteristics of chronic diseases, was the consideration that environmental factors had evident influence on them. On the contrary, acute diseases were not only characterized by their sudden and rapid appearance, but also because in them it was not possible, or at least it was not for the ancient doctors, to establish a close correlation between life habits and the genesis of the disease, something that was verifiable in the case of chronic diseases. In these, in fact, prolonged disorders in the diet or in any other aspect of life have an obvious nosogenic effect. This is the case of excessive eating or sedentarism in the development of diseases such as obesity or diabetes.

The case of COPD is particularly significant. Like most respiratory diseases, it is closely related to substances that are introduced into the lungs when breathing. In the specific case of COPD, with those coming from the use of tobacco. In other lung diseases, these are other products present in the atmosphere. This explains why many lung diseases are relatively modern and are linked to industrial development, the increase in fossil fuels, air pollution in cities, etc. The natural history of COPD has been associated with the introduction of tobacco in the habits of Western culture, after the discovery of America. The description of tobacco smoking given by the doctor and botanist Francisco Hernández in the notes of his scientific expedition to New Spain (1571-1577) is classic: *"the sense of sorrows and works is blunted, and it completely invades the spirit as a rest for all faculties, which could be called an almost inebriety"*. [118]. This made its use spread rapidly, although the greatest increase began in the late nineteenth century, because of mechanization and industrialization of both harvesting and marketing. In fact, mass consumption of tobacco has taken place in the twentieth century. The pioneering studies by Richard Doll and Bradford Hill [119-121] pointed out to the carcinogenic effect of tobacco smoking, that was verified even in the non-smoking wives of male smokers [122]. From then on, its worldwide consumption began to decrease.

The correlation between tobacco use and lung cancer is now evident, but not so of tobacco use and other lung diseas-

es. Moreover, there is a widespread belief that in those who do not develop cancer, tobacco use is harmless, so that almost all will end up suffering some form of lung disease, COPD, chronic respiratory failure, etc...

Chronic diseases have been considered since ancient times as "moral diseases". The moral adjective has here the etymological sense that the term possesses in Latin, of "habit" or "custom". They are called moral diseases because their appearance and development are closely linked to the disorders of life habits, or customs. According to a very ancient tradition, negative habits of life are called "vices", and their opposites are called "virtues". This is why we speak, for example, of the "vice of smoking".

Ancient medicine did not have great diagnostic or therapeutic means, but it did promote the development of healthy lifestyles in human beings. This explains the importance of "hygiene", especially "private" hygiene. A very significant characteristic of the medicine of the last two centuries is that the so-called "public hygiene" has developed spectacularly, but with a certain neglect of the "private hygiene". From medieval times until the end of the 18th century, this consisted of regulating the six factors included in what was known as the catalogue of "sex res non-natural" (six non-natural things): the environment, food and drink, movement and rest, sleep and wakefulness, excretions and secretions, and, finally, mood affections [123, 124].

Physicians tried to regulate these aspects of people's lives, their diet, physical exercise, rest, etc. It was a whole program of health education, which for cultural reasons has lost its millenary validity, so that certain chronic diseases due to poor diet, little physical exercise, use of toxic substances, pollution of the atmosphere and workplaces, etc., have grown exponentially. This explains why the great progress of medicine has been due to the better control of acute diseases, rather than to the success in the management of chronic diseases. Quite a paradox. The emergence of very efficient therapies and the attention paid to public hygiene has led to the neglect of private hygiene, a fundamental aspect, if not the most important, of health education.

Conclusion:

Attention should be drawn to the importance of health education in the field of chronic diseases. Many of them are the result of our cultural habits, which is why a new "health culture" needs to be promoted, in order to manage them properly. An objective of institutions such as the Health Sciences Foundation should be to contribute to the promotion of this new culture, through the elaboration of "Health Education Guides". In the same way that there are "Clinical Guides", aimed at professionals, there should be others that aim to educate the population in healthy lifestyle.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Mª Eulalia Valencia[1]
Rocío Montejano[1]
Victoria Moreno[1]
Luz Martín Carbonero[1]
José Ignacio Bernardino[1]
Lucía Serrano[2]

Infección por *Helicobacter pylori* en la población VIH+: una comorbilidad en la que pensar

[1]Servicio de Medicina Interna-Unidad de VIH. Hospital Universitario La Paz-IdiPaz. Madrid
[2]Investigadora asociada Hospital Universitario La Paz-IdiPaz. Madrid

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RESUMEN

Introducción. Las alteraciones gastrointestinales, son frecuentes en VIH+. *Helicobacter pylori* puede ser una causa infradiagnosticada.

Material y métodos. Se realizó una búsqueda retrospectiva de pacientes VIH+ con infección por *H. pylori* entre enero de 1998 hasta diciembre de 2017.

Resultados. Se incluyeron 132 pacientes. La dispepsia fue la sintomatología más frecuente. Un 88,5% tuvo gastritis crónica atrófica. Se consiguió la erradicación en 102 (77,3%). La curación fue más frecuente con pauta cuádruple (p=0,004) y en los más jóvenes (p=0,041).

Conclusión. La infección por *H. pylori* podría ser responsable de manifestaciones digestivas inespecíficas en los pacientes VIH+.

Palabras clave: *Helicobacter pylori*, VIH, tratamiento antirretroviral

Helicobacter pylori infection in the HIV + population: a comorbidity to think about

ABSTRACT

Introduction. Gastrointestinal disorders are frequent in HIV+. *Helicobacter pylori* may be an underdiagnosed cause.

Material and methods. Patients with HIV and *H. pylori* were described since January 1998 up to December 2017

Results. A total de 132 patients were included. The most frequent symptom was dyspepsia. 88.5% had chronic atrophic gastritis. Eradication was achieved in 102 (77.3%). Healing was more frequent with quadruple regimen (p=0.004) and in the youngest (p=0.041).

Conclusion. *H. pylori* infection could be responsible for nonspecific digestive manifestations in HIV + patients

Key-words: *Helicobacter pylori*, HIV, Antiretroviral Therapy

INTRODUCCIÓN

La infección por *Helicobacter pylori* es la infección bacteriana crónica más frecuente en humanos. La transmisión es persona a persona y el mecanismo de contagio fecal oral. Una vez que se adquiere, el microorganismo persiste en el estómago y está implicado en el desarrollo de gastritis atrófica, úlcera péptica y linfoma gástrico. La sintomatología en ocasiones es inespecífica y si no se tiene un alto índice de sospecha puede no diagnosticarse o confundirse con otros procesos [1]. Por otro lado, las alteraciones gastrointestinales, en ocasiones atribuidas al tratamiento antirretroviral (TAR), son frecuentes en los pacientes con infección por el virus de la inmunodeficiencia humana (VIH) [2, 3]. Por su ubicuidad y la poca especificidad de la sintomatología, es posible que una causa infradiagnosticada de las mismas sea la infección por el mencionado *H. pylori* [4].

Presentamos a continuación una amplia serie de pacientes coinfectados por VIH y *H. pylori* atendidos en una Unidad de VIH durante los últimos 20 años.

MATERIAL Y MÉTODOS

Se realizó una búsqueda retrospectiva de pacientes VIH+ con infección por *H. pylori* atendidos en la Unidad de VIH de un Hospital terciario de Madrid desde enero 1998 hasta diciembre

Correspondencia:
Mª Eulalia Valencia Ortega
Servicio de Medicina Interna-Unidad de VIH. Hospital Universitario La Paz-IdiPaz. Madrid.
E-mail: eulalia.valencia@salud.madrid.org

de 2017. Se seleccionaron aquellos en los que el diagnóstico de la infección por *H. pylori* fue posterior al del VIH. Se describen las características epidemiológicas, clínicas, inmunovirológicas, método diagnóstico, tratamiento y evolución analizando posteriormente los factores determinantes de la erradicación o no de *Helicobacter*.

Los datos obtenidos se introdujeron en una base de datos diseñada para tal fin y el estudio estadístico se realizó con el paquete estadístico IBM SPSS Statistics 22. Las variables cualitativas se expresaron como número absoluto y porcentaje y las cuantitativas como mediana e índice intercuartílico. Para el análisis de las variables cualitativas se utilizó como prueba de contraste el test del Chi-cuadrado o el test exacto de Fisher y para las cuantitativas el test de la t-Student o Krusal-Wallis según correspondiera. Se consideraron significativos valores de p inferiores a 0,005.

RESULTADOS

Se recogió la presencia de infección por *H. pylori* en algún momento de su evolución en 142 pacientes de 3.930 en seguimiento (3,6%). De ellos, 10 fueron excluidos por ser el diagnóstico previo al de la infección por VIH. El número de casos diagnosticados cada año fue aumentando progresivamente desde un único caso en 1998 hasta 22 en 2017, siendo el 54,1% (72 pacientes) diagnosticados en los últimos 5 años. Las características clínico-epidemiológicas del global de la serie aparecen reflejadas en la tabla 1.

La dispepsia fue la manifestación clínica fundamental apareciendo en 70 pacientes (72,2%). Los principales métodos diagnósticos fueron la realización de una endoscopia oral en 78 pacientes (65%) y el test del aliento con urea marcada con 13C en 42 (35%). El hallazgo endoscópico fundamental fue la gastritis crónica atrófica que se encontró en 69 de los 78 pacientes a los que se hizo endoscopia (88,5%). En 8 pacientes de los 78 (10,2%) se encontró una hernia hiatal, en 4 (5,1%) una úlcera gástrica y en otros 4 una úlcera duodenal. Se diagnosticaron simultáneamente un carcinoma y un linfoma gástrico. Ambos pacientes fueron tratados con cirugía y quimioterapia el primero y con quimioterapia el segundo y se encuentran asintomáticos 4 y 10 años después respectivamente.

El tratamiento empleado para la erradicación del *H. pylori* fue hasta la publicación de las conclusiones de la IV Conferencia Española de Consenso sobre el tratamiento de la infección por *H. pylori* en 2016 [5] la pauta triple que asociaba omeprazol 20 mg/12 h, claritromicina 500 mg/12 h y amoxicilina 1 g/12h (OCA) durante 10 días. Posteriormente pasó a emplearse la pauta cuádruple que asocia a lo anterior metronidazol 500 mg/12h durante 14 días (OCA + metronizazol). Recibieron OCA 78 pacientes (72,9%), OCA + metronidazol 26 (24,3%) y en 24 no estaba especificada en la historia clínica cual era la pauta de tratamiento empleada. Por la gravedad de las interacciones con omeprazol, se cambió el TAR basado en rilpivirina y/o atazanavir en 14 pacientes (10,9%). En aquellos que recibían elvitegravir/cobicistat no se modificó la pauta ya que, aunque hipotéticamente se podrían aumentar las concentraciones de claritromicina, la duración del tratamiento de *Helicobacter* es breve y la interacción no está claramente definida siendo, además, de carácter moderado [6]. Tampoco se modificó el TAR en los que recibían darunavir/ritonavir o darunavir/cobicistat si bien fueron monitorizados de forma estrecha por la posibilidad de aparición de toxicidad de la claritromicina al producirse aumento de su área bajo la curva [6, 7].

Tabla 1 **Características clínico-epidemiológicas de los 132 pacientes coinfectados por *Helicobacter pylori* y VIH**

	n (%)
Sexo varón/mujer	103/29 (78/22)
Edad (años)	47 (40-53)
Raza caucásica	121 (91,7)
Factor de riesgo para transmisión del VIH	
Parenteral	38 (28,8)
Sexual	82 (62,2)
Otra	7 (9)
Grupo CDC	
A	83 (62,9)
B	24 (18,2)
C	24 (18,2)
Años de evolución de la infección por VIH	14 (7-22)
Hepatitis crónica por virus B (HBsAg+)	6 (4,5)
Hepatitis crónica por virus C	14 (10,6)
TAR al diagnóstico	
Inhibidor de la proteasa	27 (20,5)
No Análogo	41 (31,1)
Inhibidor de la integrasa	33 (25)
Pauta sin nucleósidos	15 (11,3)
Sin TAR	14 (10,6)
Carga viral <50 copias/mL	112 (84,8)
Con TAR	110/112 (98,2)
Linfocitos CD4+/mm^3 al diagnóstico de *H. pylori*	669 (426-860)
Nadir de linfocitos CD4+/mm^3	242 (152-353)
Sintomatología	
Dispepsia	70 (72,2)
Epigastralgia	43 (43,9)
Pirosis	42 (42,9)
Flatulencia	21 (21,4)
Otras	20 (20,4)
Tratamiento	
Triple (OCA)	78 (59)
Cuádruple (OCA + metronidazol)	26 (19,7)
Otros	3 (2,8)
No recogido	25 (18,9)

Variables cualitativas: N (%); Variables cuantitativas: mediana (IQR)
OCA: omeprazol, claritromicina y amoxicilina

Tabla 2 **Diferencias encontradas entre los pacientes en los que se consiguió la erradicación de *Helicobacter pylori* y los que no**

	Erradicación	
	SI n (%) = 102 (77,2)	NO n (%) = 30 (22,7)
Sexo varón/mujer	82 (80,4) /20 (19,6)	21 (70,0) /9 (30,0)
Edad (años)[a]	46 (40-51)	50 (44-55)
Raza caucásica	94 (92,2)	27 (90,0)
Transmisión		
Parenteral	29 (29,3)	9 (32,1)
Sexual	65 (65,6)	17 (60,7)
Otra	5 (5,1)	2 (7,1)
Grupo CDC		
A	65 (64,4)	18 (60,0)
B	19 (18,8)	5 (16,7)
C	17 (16,8)	7(23,3)
Años de evolución de la infección por VIH	14 (8-21)	14 (7-25)
Hepatitis crónica por virus B (HBsAg+)	5 (5,0)	1 (3,3)
Hepatitis C crónica por virus C	10 (10,0)	4 (13,3)
TAR al diagnóstico		
Inhibidor de la proteasa	22 (24,4)	5 (20,0)
No Análogo	34 (37,8)	7 (28,0)
Inhibidor de la integrasa	25 (27,8)	8 (32,0)
Sin nucleósidos	9 (10,0)	5 (20,0)
No TAR	11	3
Carga viral < 50 copias/mL	86 (87,8)	26 (92,9)
Con TAR	85 (97,7)	24 (100)
CD4+/mm^3 al diagnóstico de *H. pylori*	683 (423-864)	585 (430-845)
Nadir de linfocitos CD4+/mm^3	249 (154-357)	235 (121-341)
Sintomatología		
Dispepsia	49 (69,0)	20 (80,0)
Epigastralgia	31 (43,1)	12 (48,0)
Pirosis	29 (40,3)	13 (52,0)
Flatulencia	15 (20,8)	5 (20,0)
Otras	17 (23,9)	3 (11,5)
Tratamiento[b] (recogido en 104 pacientes)[a]		
Triple	59 (76,6)	18 (23,4)
Cuádruple	23 (85,2)	4 (14,8)
Otros	0 (0)	3 (100)

Variables cualitativas: N (%); Variables cuantitativas: mediana (IQR) [a]p<0,05
[b]3 pacientes tratados con pauta triple inicialmente sin respuesta, fueron posteriormente tratados con pauta cuádruple y buena respuesta.

Se consiguió la erradicación de *Helicobacter* con la primera pauta de tratamiento utilizada en 102 pacientes (77,3%). La confirmación de la erradicación se realizó repitiendo el test del aliento en todos los casos excepto en 3 pacientes en los que hubo que repetir la endoscopia para control de lesiones ulcerosas. El sexo, la conducta de riesgo, la raza, el estadio del CDC, la sintomatología, la presencia de hepatopatía crónica por virus B o C, la carga viral del VIH, el nadir y el recuento de CD4+ en el momento del diagnóstico de la infección no influyeron en la erradicación. La curación fue más frecuente en los pacientes tratados con pauta cuádruple (p=0,004) y la edad media de los curados fue significativamente menor (p=0,041). En la tabla 2 se muestran las diferencias encontradas entre los pacientes en los que se consiguió la erradicación y los que no.

DISCUSIÓN

La prevalencia de la infección por *H. pylori* entre los pacientes con VIH es variable y oscila entre el 18 y el 30%, según la población estudiada, si los pacientes recibían o no TAR y el área geográfica [8]. Algunos autores han descrito que es significativamente más baja que en la población general y que además disminuye a medida que los CD4+ disminuyen, siendo los pacientes con mejor situación inmunológica los más susceptibles a la infección [9]. Al igual que en esos casos, en nuestra serie el 70% de los pacientes tenía > 500 linfocitos CD4+ por mm^3 en el momento del diagnóstico y sólo 39% había tenido un nadir < 200 mm^3. Por otro lado, de forma global, en nuestra serie, el número de pacientes con coinfección por *H. pylori* fue pequeño (<4%) probablemente debido al bajo índice de sospecha en los años iniciales en los que la mayoría de los síntomas digestivos se atribuyeron a toxicidad del TAR. Las manifestaciones clínicas son habitualmente inespecíficas y, en ocasiones, como verosímilmente ocurrió en esta serie, pueden confundirse con toxicidad gastrointestinal secundaria al TAR ya que su presencia es, desde los inicios de su utilización, uno de los motivos fundamentales para efectuar un cambio de tratamiento [2-4]. En el momento actual, los efectos secundarios de los antirretrovirales han disminuido significativamente, aunque no es excepcional que haya pacientes que refieren molestias digestivas que persisten a pesar de que se cambie el TAR [2, 3]. En estos casos y en los enfermos que presentan de forma crónica manifestaciones dispépticas, epigastralgia, flatulencia o halitosis estaría indicada la realización de pruebas diagnósticas encaminadas a detectar la presencia de *H. pylori* [10]. De todas formas, por la mayor supervivencia de la población con infección por VIH y la mejora global de la situación inmunológica probablemente asistamos en los próximos años a un aumento de los casos, al igual que sucede con otros procesos, existiendo ya grupos que han detectado la presencia de *Helicobacter* en el 10-30% de sus pacientes [4, 8, 11].

Cuando la realización de una endoscopia está indicada por la existencia de hemorragia digestiva alta, antecedentes de linfoma o historia familiar de carcinoma gástrico, la técnica diagnóstica de primera elección es el test de la ureasa en una biopsia antral [10]. Sin embargo, no debe realizarse como prueba diag-

nóstica de rutina ya que un test del aliento positivo confirma la presencia de *Helicobacter* al ser excepcionales los falsos positivos [12, 13]. La endoscopia, por otro lado, puede detectar procesos asociados [14, 15] como sucedió en 2 de nuestros pacientes en los que se detectó un linfoma y un carcinoma gástrico. En nuestra serie se ha realizado en más ocasiones la endoscopia porque en las épocas iniciales se consideraba la prueba de elección, no generalizándose el uso del test del aliento hasta ya muy avanzados los años 2000. En la población general la imagen endoscópica es normal en aproximadamente el 50% de los casos. Por el contrario, en los pacientes con infección por VIH pueden existir alteraciones mucosas en un número más elevado de sujetos ya que la interacción entre *Helicobacter* y el VIH puede alterar la fisiopatología del primero [16], produciendo, como en nuestra serie, gastritis crónica en más del 75% de los casos.

Algunos autores han encontrado una peor respuesta al tratamiento frente a *H. pylori* en pacientes con infección por VIH con profunda inmunodepresión [4, 11]. Con las limitaciones inherentes a ser un estudio retrospectivo y sin grupo control, nosotros observamos que la situación inmunovirológica no influyó en la erradicación de la enfermedad, siendo mejor la respuesta en los pacientes más jóvenes y en los que se empleó la pauta cuádruple, que hoy por hoy es el tratamiento de elección en cualquier población y localización geográfica [5, 17-19].

En resumen, la mejora de la situación inmunológica y la existencia de un mayor índice de sospecha ha podido condicionar un aumento en la frecuencia del diagnóstico de *H. pylori* en los últimos años. Esta infección podría ser responsable de algunas de las manifestaciones digestivas inespecíficas que en ocasiones presentan los pacientes VIH+. La búsqueda activa de este patógeno podría contribuir, por tanto, a diferenciar si esas manifestaciones son secundarias a toxicidad del TAR o si por el contrario son debidas a la existencia de una coinfección *H. pylori*/VIH. La utilización de pauta cuádruple parece ser más adecuada para la erradicación de la infección. De cualquier forma, son necesarios más estudios para evaluar de forma correcta la historia natural de la infección por *H. pylori* en esta población para determinar si la presencia del VIH condiciona una evolución diferente a la que se observa en la población general, aunque la situación inmunovirológica sea buena.

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CONFLICTO DE INTERESES

Los autores declaran que no presentan ningún conflicto de intereses en relación con este estudio.

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Letter to the Editor

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Arcobacter butzleri and intestinal colonization

Gemma Jiménez-Guerra[1*]
Isabel Casanovas Moreno-Torres[1*]
Teodora Diana Moldovan[2],
José María Navarro-Marí[1]
José Gutiérrez-Fernández[1,2]

[1]Departamento de Microbiología, Hospital Universitario Virgen de las Nieves- Instituto de Investigación Biosanitaria de Granada. Granada.
[2]Departamento de Microbiología, Facultad de Medicina, Universidad de Granada- Instituto de Investigación Biosanitaria de Granada. Granada.

* These authors contributed equally to this work

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Sir,

Arcobacter genus includes moderately curved Gram-negative bacilli, whose dimensions are comprised between 0.2 and 0.4µm of width and 1 to 3.0µm of length. The characteristic movement of these microorganisms around their own axis is also known as the 'corkscrew-like motion'. They show adequate growth in blood-enriched media, but they can multiply in many others. Their identification through the phenotypic test results difficult due to their low metabolic activity and sometimes, when using this procedure, *Campylobacter* spp. cannot be differentiated, thus its presence remaining underestimated [1]. Nowadays their identification (as genus or species) is usually performed using mass spectometry or molecular biology techniques [2]. *Arcobacter* is closely related to the *Campylobacter* genus, both being members of the *Campylobacteriaceae* family. Their main differences are the increased oxygen tolerance and the ability to grow at lower temperatures [3, 4]. Since 2017, the *Arcobacter* genus encompasses a total of 26 species that have been isolated around the planet, mainly from meat and dairy products, but also from vegetables or seafood [5, 6]. Species of the Arcobacter genus are the fourth most encountered bacteria that can be isolated from stool cultures (from patients with diarrhea) in countries like Belgium and France [7], for that reason being considered as a new emerging pathogen and as a possible zoonotic pathogen [8]. Four species have been recorded as pathogenic for humans: *A. butzleri, A. cryaerophilus, A. thereius* and *A. skirrowii*, and the infection produced by the first one being manifested by acute persistent diarrhea, nausea, vomiting and intestinal rhythm disturbances, although cases of bacteremia not accompanied by diarrhea have been, as well, described [7, 9-11]. No bloody diarrhea episodes, as in the cases of infections by *Campylobacter* spp., have been reported. *Arcobacter* spp. possesses a great ability to adhere and invade the intestinal epithelium and other parts of the human body [6] leading, in some occasions, even to peritonitis. The first reported case of peritonitis caused by *Arcobacter* took place in 2013, when a female patient that was carrying a peritoneal dialysis catheter, acquired an infection that was not associated with gastrointestinal symptoms [12]. Although the person-to-person transmission was considered, most of the cases have been linked to the consumption of spoiled food [4, 9], this being also the cause of sporadic epidemic outbreaks [13]. In pig and bovine livestock, *Arcobacter* isolates were associated with mastitis and abortion, and it was often found as part of the normal microbiota of healthy animals [14], predominantly in birds (wild and domestic), therefore meaning that they could be an important reservoir, but it has never been reported in humans.

The aim of this study was to describe their presence in a patient, as colonizing microbiota. In February 2019, an 86-year-old female patient was hospitalized at the Traumatology and Rehabilitation Center of the Hospital Universitario Virgen de las Nieves, in Granada, in order to undergo a surgery for the implantation of a partial hip prosthesis, after a subcapital femoral fracture.

Her clinical history consisted of arterial hypertension, hypercholesterolemia, osteoporosis, Sjögren syndrome and rosacea. She was in treatment with bromazepam, amlodipine, omeprazole, ramipril, acetylsalicylic acid and she had ciprofloxacin allergy.

During former hospitalizations, she spent a long period of time in an intermediary-care center and, as it is established in the internal protocol, she previously underwent the screening for the multidrug-resistant microorganisms' colonization, which included the analysis of the colonies obtained from a rectal swab. This sample was sown following the internal protocol, in the chromogenic media CHROMID® ESBL (Bi-

Correspondence:
José Gutiérrez-Fernández.
Servicio de Microbiología. Hospital Universitario Virgen de las Nieves.
Avenida de las Fuerzas Armadas, 2. E-18012 Granada, España.
E-mail: josegf@ugr.es

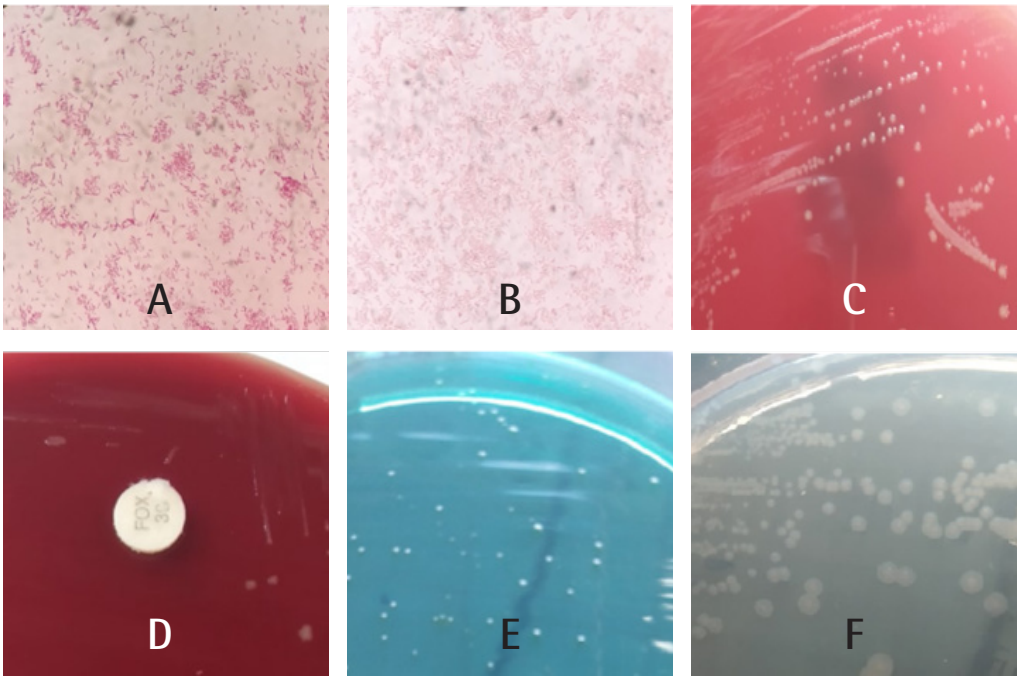

Figure 1 | **Microbiological study of the *Arcobacter butzleri* colony through Gram staining with fuchsin (A) and safranin (B), and its growing in the Columbia blood agar with CO_2 (C), Campy BAP agar (D), HK agar (E) and CIN agar (F).**

oMérieux, Spain) and CHROMID® MRSA SMART (BioMérieux). The first one is used for the detection of extended-spectrum beta-lactamase producing bacteria and, the second one, for the detection of methicillin-resistant *Staphylococcus aureus*. After 24h of incubation in aerobic atmosphere at 37ºC, only in the chromogenic medium for ESBL, some green, translucent, point-shaped, round and convex colonies appeared and from these, the species identification was performed using the MALDI-TOFF mass spectrometry (Bruker Daltonics, Germany), resulting in the recognition of *Arcobacter butzleri* in the first four positions, with a score of 1.94 for the first, and 1.79 for the last one. A microbiological study was performed to this isolate (figure 1), which included the Gram staining, with fuchsin and safranin, and its sowing in the Columbia blood agar incubated in CO_2 (Becton Dikinson, Spain), in Campy-BAP agar in microaerophilic conditions, HK agar, CIN agar, XLD agar, McConkey agar and URISELECT4 (BIORAD, US), at 37ºC. No growth was identified in the last three media after 24-48h of incubation. Its antibiotic susceptibility was, as well, studied employing the E-test (MIC Strip, Liofilchem, Itlay) in Mueller-Hinton blood agar (Becton Dickinson) incubated in CO_2. The obtained results are expressed in mg/L: tetracycline 3; ciprofloxacin 0.064; trimethoprim/sulfamethoxazol >32; ampicillin 64; azithromycin >256; cefoxatime >16/ cefotaxime-clavulanic acid >1; ceftazidime 3/ ceftazidime-clavulanic acid >4; cefotetan >32/ cefotetan-cloxacillin >32; and imipenem 2. The carbapenemase production was tested through the colorimetric assay Rapidec® Carba NP (BioMérieux), immunochromatography (Carba NG-Test, NG Biotech, US and OXA-23 K-Set, CorisBioConcept, Belgium) and Carba PCR (GeneXpert, Cepheid, US), and the results were negative in all the cases. The Nitrocefin beta-lactamase assay (Oxoid, UK) also turned out negative. After the isolation of this microorganism, the clinical history of the patient was reviewed, but no signs or symptoms of infectious enteritis were registered whatsoever. The patient not received antibiotherapy for treatment, the presence of *A. butzleri* was considered to be colonization, and she was discharged with no incidents during the following week. She only returned for the ordinary post-operatory check-ups.

Currently, there is not much data regarding the humans' colonization by the *Arcobacter* spp., and the knowledge is crucial for cases like these, when an elderly patient with such grade of immunodeficiency as the one that the Sjögren syndrome produces becomes a carrier and the microorganism does not seem to cause any harm. Even though our patient did not report any symptoms or signs during the previous months, it has been described that in patients suffering from different autoimmune diseases, the intestinal rhythm disturbances appear more frequently, being a condition that could have obscured the presence of this microorganism. Regarding a possible environmental contamination while performing the colonization study, it is important to mention that this is excluded by the consulted bibliography, since it alludes to the bacterial detection in human and animal feces as either producing gastrointestinal manifestations [6] or not [15].

The most frequently encountered pathogens producing

infectious gastroenteritis in our media are *Campylobacter* and *Salmonella* [16], but also other potential pathogens were described [17], and they present a high percentage of strains that are susceptible to ciprofloxacin [18]. Therefore, for the majority of the cases of bacterial diarrhoea, ciprofloxacin is one of the best treatment options even though more than 10% of the Arcobacter spp. isolates from patients with diarrhoea can be resistant [8]. In the case of our patient, even if she developed symptoms, she would never be treated with this antibiotic, due to her allergy to the fluoroquinolones, and she would probably receive tetracycline instead, due to the fact that the MIC for beta-lactams was elevated.

In elderly patients with any known underlying disease, and especially in those with autoimmune disorders, we must take into account that the behaviour of the intestinal microbiota can show substantial variations if compared to the normal population, this possibly leading to an immunomodulation that could preserve certain species for extended periods. For this reason, when a microorganism is encountered and it is already known as pathogenic but it is not causing any illness, we should remain alert.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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Carta al Director

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Berta Pino Calm[1]
Laura Martínez-García[2]
Concepción Beltrán Tacoronte[1]
Julia Alcoba Florez[1]

Infradiagnóstico de linfogranuloma venéreo

[1]Unidad de Microbiología y Parasitología. Servicio de Análisis Clínicos Hospital Universitario Nuestra Señora de Candelaria
[2]Servicio de Microbiología Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria, Madrid.

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Sr. Editor: *Chlamydia trachomatis* (CT) es la principal infección de transmisión sexual (ITS) a nivel mundial y va en aumento cada año [1]. Los serovares L1, L2 y L3 invaden las capas de tejido conectivo submucoso tras un período de incubación de 3-30 días, aparece una pápula indolora que puede ulcerarse y posteriormente invadir el tejido linfático causando linfogranuloma venéreo (LGV) [2].

Esta enfermedad era propia de áreas tropicales y subtropicales, e infrecuente en Europa antes de 2003, cuando la mayoría de los casos eran importados [3]. Desde 2003 esta infección ha alcanzado una distribución más amplia y actualmente está lejos de ser controlada y con probabilidades de establecerse en la población europea [4]. En el último informe del ECDC, las cifras están subestimadas ya que Holanda, Francia y Reino Unido, son responsables del 86% de los casos y en otros países los datos son muy escasos. Esta disparidad es consecuencia por un lado de la escasa implementación de los sistemas de genotipado para la detección de los serovares L1-L3 [1].

Existe un patrón epidemiológico bien definido, suelen ser hombres que practican sexo con hombres (HSH) de entre 35 y 44 años y fuertemente asociado a la infección por el virus de la inmunodeficiencia humana (VIH) [1]. También está documentada la asociación entre LGV y otras ITS [5].

Desde enero de 2019 en el servicio de Microbiología del Hospital Universitario Nuestra Señora de Candelaria está implantada una técnica basada en la reacción en cadena de la polimerasa (PCR) multiplex a tiempo real [Allplex Genital ulcer Assay(Segeene®)], que detecta 7 patógenos productores de úlceras genitales[Citomegalovirus, *Virus herpes* simple 1 y 2 (VHS), *Virus Varicela Zoster*, *Treponema pallidum*, *Haemphilus ducrey* y Linfogranuloma venéreo (L1-L3)]. Desde su puesta en marcha, se han detectado 3 casos.

Correspondencia:
Berta Pino Calm
Unidad de Microbiología y Parasitología. Servicio de Análisis Clínicos
Ctra. del Rosario, 145, 38010 Santa Cruz de Tenerife. España Hospital Universitario Nuestra Señora de Candelaria.
Tlfno: 922 602 239
E-mail: bpinocalm@gmail.com

Todos los casos eran HSH, de mediana de edad 43 años (24-55) e infectados por el VIH en tratamiento.

En el primer caso, el paciente presentaba una fisura anal atípica, a filiar junto con rectorragia y condilomas. En el proceso quirúrgico se observó una lesión ulcerosa en el canal anal muy friable y sugestiva de proctitis.

El segundo caso, el paciente tenía una lesión perianal no supurativa, no dolorosa de unos 15 días de evolución junto con aparición de adenopatías regionales.

Y en el tercer caso, el paciente presentaba rectorragias y dolor abdominal de varias semanas de evolución. Posteriormente se le realizó colonoscopia con toma de biopsia por lesión ulcerosa inespecífica que se estudio para ITS.

Las muestras rectales recibidas, fueron procesadas para cultivo bacteriológico y detección de ácido nucleicos mediante la PCR de Allplex STI-7(Segeene®) de CT, *Neisseria gonorrhoeae* (NG), *Mycoplasma hominis* (MH), *Mycoplasma genitalium* (MG), *Ureaplasma urealyticum* (UU), *Ureaplasma parvum* (UP), *Trichomonas vaginalis* (TV). Las muestras de úlceras se estudiaron mediante la PCR de Allplex Genital ulcer Assay.

Con la colaboración del servicio de Microbiología del Hospital General Universitario Ramón y Cajal (Madrid), se estudiaron las regiones *pmpH* y *OmpA* con posterior secuenciación para conocer las serovariantes de LGV (tabla 1).

En todas las muestras rectales/anales se detectó CT mediante la PCR Allplex STI-7 y LGV mediante Allplex Genital ulcer Assay.

Los dos primeros casos tuvieron coinfecciones por otro patógeno causantes de ITS, el primero de ellos presentaba coinfección con VHS tipo 2, MH, genotipos de alto riesgo de virus del papiloma humano (VPHhr) 39 y 58 y de genotipo de bajo riesgo 11, causante de condilomas. El segundo caso presentó coinfección con UU y VPHhr 68. No se encontraron coinfecciones con virus de hepatitis o *Treponema pallidum*.

Tabla 1 **Serovariantes de los tres casos.**

	pmpH	*OmpA*
Paciente 1	LGV	D
Paciente 2	LGV	L2
Paciente 3	LGV	Variante L2b

Todos fueron tratados con doxiciclina 100 mg, oral durante 21 días, resolviéndose la clínica.

Los resultados de los serovares, L2 y L2b son los más frecuentes encontrados en Europa [3]. En cuanto al serovar presente en el paciente 1, lo más probable es que se trate de una recombinación entre un serogrupo L y D [6]. Este serovar se ha asociado a patrones de transmisión en HSH [7].

Al encontrar estos nuevos casos, queremos remarcar la importancia de conocer la epidemiología local y recomendar la necesidad de implementar plataformas diagnósticas que permitan la detección de LGV; así como fomentar una búsqueda activa en aquellos pacientes con clínica sugestiva de proctitis, estreñimiento, rectorragia, leucocituria y urocultivo negativo en hombres jóvenes, o dolor abdominal de probable origen ginecológico en mujeres jóvenes. Además, se debe tener en cuenta los factores de riesgo como VIH y prácticas sexuales de HSH.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses

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Juan Rodríguez-García[1]
Rafael Fernández-Santos[2]
Enrique Ruiz de Gopegui-Bordes[3]
Olga Hidalgo-Pardo[1]

Prevención de la enfermedad neumocócica invasiva en el paciente asplénico

[1]Servicio de Medicina Preventiva. Unidad vacunación paciente inmunodeprimido. Hospital Universitario Son Espases. Mallorca. Islas Baleares. España.
[2]Servicio de Medicina Preventiva. Unidad vacunación paciente inmunodeprimido. Hospital Obispo Polanco. Teruel. España.
[3]Servicio de Microbiología. Hospital Universitario Son Espases. Mallorca. Islas Baleares. España.

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Sr. Editor: La sepsis masiva postesplenectomía es una complicación grave alcanzando una mortalidad mayor del 38% [1]. *Streptococcus pneumoniae* es el microorganismo más frecuente causando el 50-90% de estas infecciones [2]. Sin embargo, las coberturas de vacunación siguen siendo bajas [1, 3] por lo que es importante el inicio precoz de antibioterapia empírica ante la aparición de fiebre en el paciente asplénico [4].

Varón de 49 años esplenectomizado por rotura esplénica tras accidente de tráfico. Fumador de 20 cigarrillos/día sin otros antecedentes de interés. Vacunado con Prevenar-13® (VC13) a los 18 días post-esplenectomía. Acudió a Urgencias a los 8 meses post-esplenectomía por fiebre (40,3ºC) y escalofríos de comienzo brusco. Tos y expectoración verdosa en los últimos días. Exploración en urgencias sin alteraciones significativas. 22,2 x 10^3 leucocitos/µL (92,8% neutrófilos). No otras alteraciones analíticas. Posible infiltrado basal izquierdo retrocardíaco. Se pautaron antitérmicos y antibioterapia endovenosa empírica (ceftriaxona y levofloxacino) y se cursó ingreso. En los hemocultivos se identificó *S. pneumoniae* sensible a la antibioterapia pautada. El paciente evolucionó favorablemente y fue dado de alta a los 6 días. Recibió 10 días de ceftriaxona intravenosa y amoxicilina oral 5 días más.

Antes del alta recibió la vacuna antineumocócica 23 valente (VP23) y se citó en consultas para completar vacunación. No padeció nuevos episodios de infección por neumococo durante los tres años posteriores a la administración de VP23. El serotipo responsable del cuadro identificado con posterioridad al episodio fue el 10A, un serotipo cuyo antígeno capsular es exclusivo de VP23.

En esplenectomías urgentes, se recomienda la vacunación antineumocócica a partir de las 2 semanas postcirugía utilizando la pauta secuencial (VC13 seguida de VP23). El intervalo mínimo entre estas vacunas es de 8 semanas [5-9]. Sin embargo, no existe acuerdo sobre cuál es el intervalo óptimo, situándose entre el mínimo de 8 semanas recomendado por la mayoría de organismos internacionales [2, 5, 9] y 1 año o más recomendado por las Sociedades Científicas y la Ponencia de Vacunas del Consejo Interterritorial (PV-CISNS) en España [6-7].

Así el Consenso de las Sociedades Científicas Españolas cambió la recomendación en 2017 de 8 semanas a 1 año como intervalo óptimo [6, 8] y la PV-CISNS en 2018 recomendó el intervalo de 1 año entre las 2 vacunas, porque *"los intervalos de 8 semanas pueden asociarse a mayor reactogenicidad local y a una posible reducción de la inmunogenicidad respecto intervalos de 1 año o más"* [7]. Esto lo basa en el documento del *Advisory Committee on immunization Practices* (APIC) que en 2015 estableció la sustitución del intervalo 6-12 meses a 1 o más años, pero exclusivamente para adultos inmunocompetentes de 65 años o más manteniendo el intervalo de 8 semanas para todos los demás grupos de riesgo incluyendo asplénicos. Este intervalo sigue siendo el recomendado para estos pacientes por el APIC en su última actualización de 2018 [9]. Además, señala que este aumento en el intervalo recomendado para pacientes sin factores de riesgo, se basa exclusivamente en tratar de armonizar la pauta con la del paciente [de 65 o más años] que ya había recibido VP23, es decir, establecer el mismo intervalo de 1 año en la pauta VP23-VC13 y VC13-VP23 [5]. Respecto a la inmunogenicidad y reactogenicidad de los intervalos de 1 año frente a 8 semanas el APIC señala que no existe nueva evidencia ni estudios de inmunogenicidad que evalúen el intervalo óptimo entre las dos vacunas y que el único estudio en el que se comparan dos intervalos (8 semanas *vs.* 6 meses) no halló diferencias en la inmunogenicidad entre las dos pautas aunque el de 8 semanas mostró más inflamación local [5].

Debemos considerar además la ventana de riesgo para proteger contra la enfermedad causada por los serotipos exclusivos de VP23, ya que aproximadamente el 25% de la Enfermedad Neumocócica Invasiva (ENI) en adultos de España de debe

Correspondencia:
Juan Rodríguez García
Servicio de Medicina Preventiva. Unidad vacunación. Hospital Universitario Son Espases.
Carretera Valldemossa 79. 07120. Mallorca. Islas Baleares. España.
Tfno.: (0034) 871205000.
E-mail: juan.rodriguezgarcia@ssib.es

a serotipos exclusivos de VP23 respecto al 50% causada por serotipos comunes. Esta relación llega a invertirse en los últimos años suponiendo el 40,2% y 37,3% para serotipos exclusivos de VP23 y comunes respectivamente, debido a la inmunidad de grupo conseguida con la vacunación de los niños [10]. El intervalo de 8 semanas recomendado por la mayoría de Organismos de otros países [2,9], minimiza la ventana de riesgo de ENI causada por serotipos exclusivos de VP23 [5].

En el presente caso, el comienzo precoz de la antibioterapia empírica contribuyó a la evolución favorable del cuadro invasivo a pesar de la asplenia. Sin embargo, este episodio podría haberse evitado administrando VP23 de forma precoz según el intervalo mínimo de 8 semanas, si bien la mayor reactogenicidad local debe tenerse en cuenta. Mientras la investigación sobre el intervalo óptimo continúa, debería decidirse individualizadamente el momento óptimo tras VC13, para administrar VP23 y mantener una alta sospecha clínica de ENI ante la aparición de fiebre en el paciente esplenectomizado.

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CONFLICTO DE INTERESES

El primer autor ha recibido honorarios como ponente y subvenciones para actividades científicas por GSK, Pfizer y Pasteur. No existen otros conflictos de interés por parte de los autores.

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Letter to the Editor

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Laura Tabuenca Del Barrio
Marcos Mozo Cuadrado
Enrique Borque Rodríguez-Maimón
Alicia Zubicoa Eneriz
Andrés Garralda Luquín

Decreased painful visual acuity. *Corynebacterium macginleyi* blebitis-endophthalmitis infection

Complejo Hospitalario de Navarra, Ophthalmology. Pamplona (Navarra). Spain

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Sir,

A 74 year-old female presented with pain and blurred vision in her left eye since one day. As a personal records included bilateral chronic open angle glaucoma, bilateral trabeculectomy and cataract surgery in both eyes. Visual acuity (VA) was 20/40 in the right eye and light perception in the left eye. Slit-lamp examination showed a white conjunctival swelling superiorly (figure 1A) and hypopyon in anterior chamber. Fundus examination revealed a dense vitritis. Applanation intraocular pressure was 4 mmHg. Echography manifested echogenic shadows in the vitreous cavity (figure 1B). A culture of conjunctival swelling was performed and revealed *Corynebacterium macginleyi* growth. The material was cultured on Columbia agar plates supplemented with 5% sheep blood and chocolate agar for 24 h at 37°C in a 5% CO_2-enriched atmosphere and on MacConkey agar at 37°C in ambient air. The lipophilic *Corynebacterium* were identified by API Coryne system, in conjunction with API Coryne database. The antibiogram showed susceptibility to ciprofloxacin, chloramphenicol, gentamicin, tobramycin, neomycin and tetracyclines. The patient was diagnosis of infectious bleb-associated endophthalmitis in left eye. The treatment involved ceftazidime (2.25 mg/0.1 ml) and vancomycin (1 mg/0.1 ml) intravitreal injections. In addition, intensive topical antibiotics of ceftazidime and vancomycin together with topical (1 drop/8 hours) and oral (400 mg/12h) ciprofloxacin were administered. Forty-eight hours later, intravitreal injections were repeated keeping the same topical and oral treatment. The treatment was well tolerated and the pain was subsiding. One week later, when anterior pole allowed a good visualization, a washing anterior chamber and a pars plana vitrectomy were carried out. Oral ciprofloxacin was suspended and topical tobramycin, dexamethasone and ciprofloxacin (1 drop/8 hours) were instilled for one month. Finally, VA was 20/100 and a fibrous bleb was observed (figure 2).

Glaucoma is a pathology which requires surgical techniques in some patients. The trabeculectomy involves a defect in the sclera and a filtering conjunctival bleb to allow excess aqueous humour leaves out of the anterior chamber. The finality of this surgery is a reduction of intraocular pressure in patients with a medical management failure and intracameral cefuroxime is used as antibiotic prophylaxis in surgical procedure.

Blebitis with endophthalmitis is an infrequent complication after glaucoma filtering surgery which consists of an infected conjunctival bleb with anterior chamber and vitreous affection. Typically occurs months to years following surgery and usually has a devastating prognosis.

C. macginleyi is an infrequent pathogen of blebitis. To the best of our knowledge, this is the first case report of a *C. macginleyi* blebitis-endophthalmitis infection and its correct treatment is related to prevent subsequent complications.

Blebitis may be associated or not with vitreous infection. The onset is usually abrupt in cases which involve endophthalmitis: the patients presents with sudden onset of eye pain, decreased vision and red purulence bleb. This affection may be classificated in three ways: isolated blebitis, early bleb-associated endophthalmitis (BAE) or late bleb-associated endophthalmitis, which have different pathogenesis and prognosis [1].

Staphylococcus epidermidis and *Staphylococcus aureus* are the most common cause in isolated blebitis. Early BAE appears in the first month after surgery and *S. epidermidis* is the main organism implicate. Generally, it is caused by the perioperative introduction of host flora. In late BAE, that appears after one month of surgery action, *Streptococcus* species, *Haemophilus influenzae* or *Moraxella catarrhalis* are the main cause migrating through thin-walled blebs and generating a poor outcome [1].

Correspondence:
Laura Tabuenca Del Barrio
Complejo Hospitalario de Navarra, Ophthalmology.
Calle Irunlarrea s/n, 31008 Pamplona (Navarra). Spain
Phone: +34675621164
E-mail:l.tabuenca.del@navarra.es

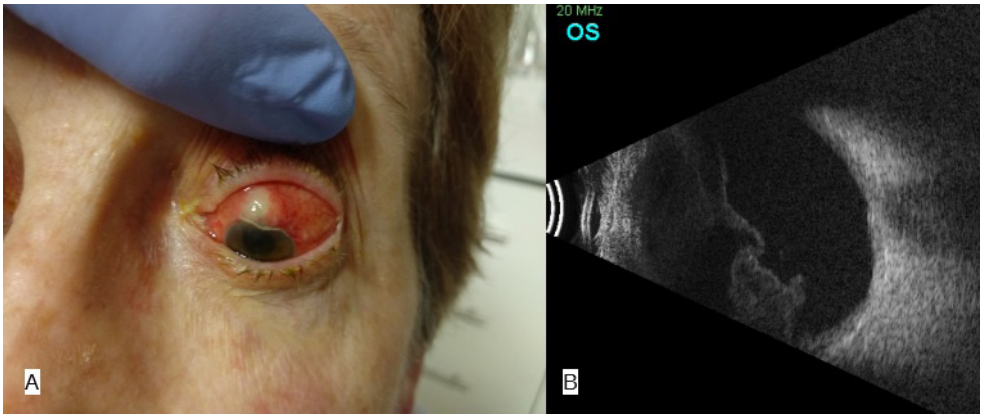

Figure 1 | **A red and purulence superior conjunctival bleb (A). Echography: Hyperechogenic shadows demonstrate dense vitritis (B)**

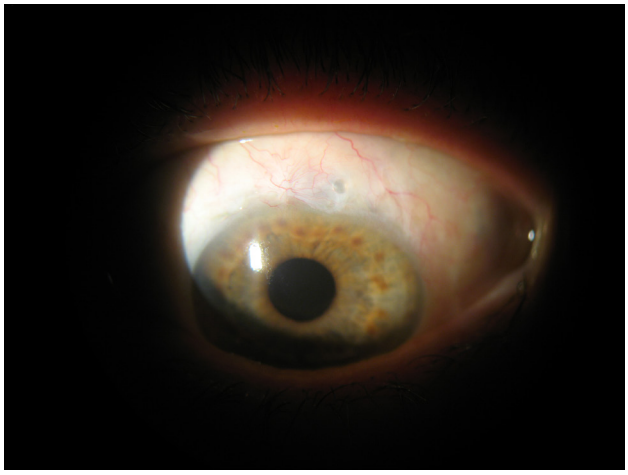

Figure 2 | **Slit-lamp photograph. Ocular surface after medical and surgical therapy. A fibrous conjunctival bleb is observed.**

Our clinical case appears two years after surgical technique, so it is a late BAE.

C. macginleyi is a lipophilic dipheroidal conjunctival Corynebacteria. It is usually a habitual resident of conjunctival flora and mainly generates conjunctivitis [2-4]. It is unsurprising that Corynebacteria generates blebitis due to the implication of conjunctival tissue in filtering glaucoma surgery [2]. In spite of this, it is the first time that this organism affects anterior chamber and vitreous too. An infected bleb culture must be obtained in all the patients.

C. macginleyi was described by Riegel et al. in the study of lipophilic *Corynebacterium* [5]. The identification of *C. macginleyi* is based on biochemical test and API Coryne (bioMèrieux) system in conjunction with API Coryne database. The results consist of positive nitrate reduction, positive alkaline phosphatase, negative pyrazinaminidase, acid production from glucose and sucrose but not from maltose [6].

A susceptibility antibiotic testing should be performed: it is usually susceptible to beta-lactams, tetracyclines, fusidic acid, glycopeptides and rifampicin [2]. Funke et al. described the susceptibility to antibiotics of *C. macginleyi* finding very low minimum inhibitory concentration values for almost all tested antibiotics, except macrolides [3].

An intravitreal vancomycin (1 mg/0.1 ml) plus ceftazidime (2.25 mg/0.1 ml) therapy is indicated in BAE. If vitreous inflammation persists, intravitreal injections may be repeated after 48 hours in the same doses and vitrectomy should be considered [7]. In our case, a favourable response with painful decreased was observed after antibiotic treatment beginning but vitrectomy was necessary to eliminate vitreous infection consequences.

The prognosis in late BAE is poor, but in our case report the large antibiotic susceptibility of *C. macginleyi* could implicate a better outcome obtaining a 20/100 final visual acuity instead of a total loss of vision.

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None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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Letter to the Editor

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Jaime Borrego-Jiménez[1]
Claudia Soria-Segarra[2]
Teodora Diana Moldovan[3]
José María Navarro-Marí[1]
José Gutiérrez-Fernández[1,3]

Use of WalkAway MicroScan system colistin well when determining the susceptibility of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* recent clinical isolates

[1]Departamento de Microbiología, Hospital Universitario Virgen de las Nieves-Instituto de Investigación Biosanitaria de Granada. Granada.
[2]Departamento de Microbiología. Facultad de Ciencias Médicas, Universidad de Guayaquil, PC, EC090112, Ecuador.
[3]Departamento de Microbiología, Facultad de Medicina, Universidad de Granada- Instituto de Investigación Biosanitaria de Granada. Granada.

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Sir,

The increasing number of multiresistant non-fermenter Gram-negative bacilli isolates has boosted the use of antibiotics, like colistin, for the treatment of the infections caused by these microorganisms [1]. Unfortunately, the assessment of the colistin ssusceptibility is not an easy task in a microbiology laboratory, thus finding a solution for this situation has become essential. It has been described that disc-diffusion and E-test methods are not reliable tools, since a high percentage of false resistance has been detected as their result [2]. Based on the EUCAST guidelines [3], the gold standard for the colistin sensitivity determination would be the broth microdilution method, even though this implies the added difficulty of the manual processing. A few alternatives can be considered, like the Sensititre (ThermoFisher Diagnostics, U.S.) and the MicroScan (Beckman Coulter, U.S.) panels but, even in these, the several performed studies have found that false resistances can appear in up to 65% of the cases [4]. Another useful method, considering the EUCAST's proposal, is the manual microdilution used in UMic test (BioCentric, France), which we are currently using in our laboratory in order to confirm the resistances that the MicroScan system has previously found. The aim of our study was to compare the automatized MicroScan and E-test (gradient diffusion) methods to the UMic manual microdilution.

A total of 23 isolates (17 *Pseudomonas aeruginosa and 6 Acinetobacter baumannii), all* proceeding from urine cultures of different clinical episodes, have been studied between April 2018 and April 2019, being all interpreted as colistin-resistant by the MicroScan system (table 1). Focusing our attention on the study of false positives (*major errors),* colistin susceptibility has been evaluated using the gradient-diffusion E-test (MIC Strip, Liofilchem, Italy) method in Müller-Hinton agar (BD, Spain) and through microdilution (UMic), which was used as the reference method. The colistin susceptibility study was carried out accordig to the manufacturers' instructions. The ATCC 27853 (American Type Culture Collection) strain of *Pseudomonas aeruginosa* was used as control.

The possible MIC ranges were ≤ 0.06 to > 64 mg/L for the manual microdilution, ≤ 2 to > 4 mg/L for the MicroScan system and ≤ 0.016 to > 256 mg/L corresponding to the E-test method. The obtained results are presented in the table 1. A MIC > 2 mg/L was obtained in 7 isolates (30.4% of the samples) through E-test method, in 4 isolates (17.4%) through manual microdilution and in 2 isolates (8.7%) using both techniques. A total of 83% of the isolates that MicroScan system identified as having a MIC ≥ 4 mg/L resulted to be susceptible (MIC ≤ 2 mg/L) after using the reference method of our laboratory, therefore meaning that the MicroScan system possesses a very low specificity. Concomitantly, the E-test method resulted not to be efficient at determining this possible resistance since its outcomes were MIC > 2 mg/L in isolates that were susceptible performing microdilution and, at the same time, it showed sensitivity in resistant isolates (false negative or *very major errors*).

The gathered data brings into question the utility of the colistin wells in these panels from MicroScan system, although maybe their negative predictive value justifies their presence. Therefore, we think that the colistin well should be reviewed in order to determine the possibility of being improved, removed or reinterpreted in the manufacturer's instructions.

For the moment, our recommendation when colistin resistance appears in non-fermenter Gram-negative bacilli, is to always perform a second interpretation, using UMic or other method, following the EUCAST's suggestions. Larger studies involving a higher number of isolates are necessary in order to reach global reliable conclusions.

Correspondence:
José Gutiérrez-Fernández.
Laboratorio de Microbiología. Hospital Universitario Virgen de las Nieves.
Avenida de las Fuerzas Armadas, 2. E-18012 Granada, España.
E-mail: josegf@go.ugr.es

Table 1 **Susceptibility to colisitin in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates.**

		MicroScan System		E-Test System		UMic System	
Isolates	Microorganisms	MIC (mg/L)	S/R	MIC (mg/L)	S/R	MIC (mg/L)	S/R
1	*A. baumannii*	> 4	R	2	S	0.06	S
2	*A. baumannii*	> 4	R	2	S	0.125	S
3	*A. baumannii*	4	R	2	S	0.5	S
4	*A. baumannii*	4	R	2	S	0.5	S
5	*P. aeruginosa*	> 4	R	1.5	S	0.5	S
6	*P. aeruginosa*	4	R	1	S	1	S
7	*P. aeruginosa*	4	R	1.5	S	1	S
8	*P. aeruginosa*	4	R	1	S	1	S
9	*A. baumannii*	4	R	0.75	S	1	S
10	*P. aeruginosa*	4	R	1.5	S	1	S
11	*P. aeruginosa*	> 4	R	1	S	1	S
12	*P. aeruginosa*	4	R	3	R	1	S
13	*P. aeruginosa*	> 4	R	1	S	1	S
14	*P. aeruginosa*	4	R	2	S	1	S
15	*P. aeruginosa*	> 4	R	6	R	1	S
16	*P. aeruginosa*	4	R	6	R	1	S
17	*P. aeruginosa*	> 4	R	0.75	S	2	S
18	*P. aeruginosa*	> 4	R	3	R	2	S
19	*P. aeruginosa*	4	R	3	R	2	S
20	*P. aeruginosa*	4	R	1.5	S	4	R
21	*P. aeruginosa*	4	R	4	R	4	R
22	*A. baumannii*	> 4	R	24	R	32	R
23	*P. aeruginosa*	> 4	R	2	S	32	R

MIC= minimum inhibitory concentration.

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None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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Carta al Director

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Estrategias para la mejora de la prescripción del tratamiento antibiótico en Urgencias

Eva Orviz[1]
Pablo Jerez-Fernández[2]
Miguel Suarez-Robles[1]
Clara Ramos-Rey[3]
Inés Armenteros[1]
María Fernández-Revaldería[4]
Juan González del Castillo[5,6]

[1]Servicio de Medicina Interna, Hospital Clínico San Carlos, Madrid, España
[2]Centro de Salud General Ricardos, Madrid, España
[3]Centro de Salud Las Águilas, Madrid, España
[4]Centro de Salud de Eloy Gonzalo, Madrid, España
[5]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, España
[6]Instituto de Investigación Sanitaria del Hospital San Carlos, Madrid

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Sr. Editor:

Hemos leído con interés el estudio realizado por Osorio et al. [1] que concluye que la prescripción de antibióticos de "Categoría Especial" en urgencias es adecuada en un 68% de los casos. Además, describen variables independientes asociadas a una prescripción adecuada como la presencia de factores de riesgo de infección por microorganismos multirresistentes (MMR), especificar el foco de la infección y señalar la gravedad del episodio. Los antibióticos analizados son los utilizados para el tratamiento de infecciones por MMR. El tema abordado nos resulta de gran interés, por lo que nos gustaría realizar algunos comentarios y ofrecer datos de los registros de la red de investigación del grupo de infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias (INFURG-SEMES).

Las infecciones suponen el 15% de las atenciones en los servicios de urgencias hospitalarios (SUH) [2]. El aumento en la esperanza de vida, la mayor supervivencia de los enfermos oncológicos y el mayor número de personas que se someten a procedimientos invasivos o reciben tratamientos inmunosupresores ha producido un cambio en el perfil del paciente "prototipo" atendido en urgencias. Presenta una mayor edad, comorbilidades y factores de susceptibilidad a infecciones por MMR [3]. Merced a estos factores, es cada vez más frecuente que en urgencias asistamos a pacientes con infecciones por MMR. Un estudio reciente del grupo INFURG-SEMES muestra como 1 de cada 4 aislamientos de muestras obtenidas en urgencias presenta un MMR [4]. El trabajo mencionado presenta un sesgo de selección, ya que no se consideran los cultivos negativos y, por otra parte, en los SUH se solicita cultivo principalmente al paciente más grave y complejo. No obstante, pensamos que este dato pone de manifiesto la magnitud del problema.

Correspondencia:
Juan González del Castillo
Servicio de Urgencias. Hospital Clínico San Carlos.
Calle Profesor Martín-Lagos s/n, 28040 Madrid.
Phone Number: (34) 91.330.37.50
FAX Number: (34) 91.330.35.69
E-mail: jgonzalezcast@gmail.com

Múltiples estudios han puesto de manifiesto una elevada frecuencia de casos en los que el tratamiento antibiótico empírico en el SUH no es correcto, cifrándolo en torno al 50% [5, 6]. En el estudio de Osorio et al. [1] la prescripción adecuada del 68% se define en base a la aplicación de la guía antimicrobiana usada en el centro. Otro trabajo español [7], utilizando también como base las guías locales, la cifra en el 62%. Sin embargo, además de esta aproximación al tratamiento adecuado basada en el seguimiento de las guías, pensamos que es conveniente analizar las prescripciones apropiadas basada en los resultados microbiológicos obtenidos posteriormente.

En este sentido, hemos realizado un sub-análisis de un registro multipropósito que incluyo los datos clínicos y analíticos de los pacientes atendidos por infección en 54 SUH de España durante 1 año y en los que se obtuvo un aislamiento microbiológico en una muestra obtenida durante su primera atención en urgencias [4]. Se incluyeron 5.460 pacientes con una edad media de 70,5 (DE 18,3) años, siendo 2.846 (52,1%) varones. Entre los aislamientos, 1.345 (24,6%) fueron considerados como MMR. Se prescribió tratamiento antibiótico con cobertura para microorganismos Gram positivos resistentes en 313 (5,7%) pacientes y para Gram negativos resistentes en 1.454 (26,6%). En este trabajo, basándonos en la susceptibilidad de la cepa aislada al antibiótico prescrito en urgencias, se determinó que en 1 de cada 5 (19,8%) pacientes se prescribió un tratamiento inapropiado. Mediante un análisis de regresión logística hemos identificado las variables que se asocian de manera independiente a la prescripción apropiada de antimicrobianos (tabla 1). Al igual que en el trabajo presentado por Osorio et al. [1], la gravedad, definida mediante distintas escalas clínicas [8], se asocia a una mayor probabilidad de tratamiento adecuado. En nuestros análisis, el tener infección del tracto urinario, infección intraabdominal y elevada comorbilidad también se asocian a una mejor prescripción.

Respecto al diagnóstico etiológico, se conoce bien la dificultad con la que nos encontramos en los SUH para disponer de él [9]. Esto conlleva que la prescripción se realice basán-

Tabla 1 **Variables independientes asociadas con la prescripción apropiada de tratamiento antibiótico.**

Variable	β	OR (IC 95%)	p
Gravedad[a]	1,826	1,532-2,178	<0,001
Índice de Charlson ≥3	1,255	1,038-1,517	0,019
Antecedente de infección por MMR	1,097	1,024-1,176	0,009
Infección urinaria	2,377	1,995-2,832	<0,001
Infección intraabdominal	1,464	1,128-1,900	0,004

MMR: microorganismo multirresistente; OR: odds ratio; IC: intervalo de confianza
[a]Gravedad se define si el paciente presenta durante la primera evaluación un incremento de la escala SOFA ≥2 puntos respecto al basal, una puntuación en la escala NEWS ≥5, o un qSOFA ≥2 puntos.

donos en la gravedad, el modelo de infección, las resistencias locales y en la valoración de los factores de riesgo para MMR. El problema de estas escalas de riesgo es que son múltiples, diferentes para cada modelo de infección e incluyen factores comunes para distintos patógenos, lo que dificulta la toma de decisiones. Además, los artículos publicados se limitan mayoritariamente a describir los factores de riesgo asociados, sin proporcionar una evaluación del riesgo basada en el número y el peso de los criterios que el paciente puede cumplir [10]. El grupo INFURG-SEMES ha desarrollado un modelo predictivo de infección por MMR, la escala ATM (Assessment of Threat for Multidrug resistance microorganisms) [4], accesible en https://atmscore.urgenciasclinico.com, que utiliza variables disponibles durante la primera atención y que clasifica los pacientes en 6 grupos de riesgo para ayudar a la decisión sobre ampliar o no el espectro antimicrobiano en la terapia empírica.

Sin embargo, pensamos que para afrontar el reto de la prescripción de antibioterapia en los SUH debemos apoyar estrategias de diagnóstico microbiológico rápido, que podrían ser de aplicación en pacientes seleccionados, utilizando las escalas clínicas para identificar a los pacientes con bajo riesgo de infección por MMR y aplicando las nuevas técnicas de diagnóstico molecular en aquellos de riesgo intermedio o alto. De esta manera podríamos mejorar la adecuación del tratamiento antibiótico, limitar la prescripción de antimicrobianos de amplio espectro y hacer sostenible la inversión en estas nuevas técnicas diagnósticas.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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