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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
28040 Madrid

Atención al cliente
Teléfono 91 394 15 12
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Sumario

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Manuel Martínez-Sellés[1]
Luis Prieto-Valiente[2]

Clinical study types and guidance for their correct post-pandemic interpretation

[1]Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERCV. Universidad Europea, Universidad Complutense. Madrid. Spain
[2]Cátedra Internacional de Análisis Estadístico y Big Data. Universidad Católica de Murcia (UCAM). España. ADA.rt Advanced Data Analysis. Research and Teaching. SCIB

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ABSTRACT

Randomized clinical trials (RCTs) are key to the advancement of medicine and microbiology, but they are not the only option. Observational studies provide information on long-term efficacy and safety, are less expensive, allow the study of rare events, and obtain information more quickly than RCTs. On the other hand, they are more vulnerable to confounding factors.

Prospective exploratory pilot studies share many aspects with RCTs but are not subject to supervision by external commissions or mandatory registration. Multitesting can pervert the balance of publications in favor of the desired effect. Bonferroni's reasoning shows that if 10 studies are performed with an ineffective antibiotic, the probability that at least one will show P <0.05 might be 40%**.** Scenarios in which there is intensive pressure to perform research, such as the recent pandemic, might result in many research teams trying to study the effect of an antimicrobial. Even if the drug has no efficacy, if 100 research teams conduct a study to assess its usefulness, it might be virtually certain that at least one will get a P value <0.05. If the other studies (with P >0.05) are not published, the scientific community would consider that there is strong evidence in favor of its usefulness.

In conclusion, RCTs are a very good source of clinical information, but are not the only one. The systematic registration of all research can and should be applied to all types of clinical studies.

Keywords: methodology, statistics, clinical trials.

Correspondence:
Manuel Martínez-Sellés.
Cardiology Service, Hospital General Universitario Gregorio Marañón
C/ del Dr. Esquerdo 46, 28007, Madrid. Spain
E-mail: mmselles@secardiologia.es

Tipos de estudios clínicos y pautas para su correcta interpretación post-pandemia

RESUMEN

Los ensayos clínicos aleatorizados (ECA) son claves en el avance de la medicina y la microbiología, pero no son la única opción posible. Los estudios observacionales proporcionan información sobre la eficacia y la seguridad a largo plazo, son menos costosos, permiten estudiar eventos poco frecuentes y obtener información más rápido que los ECA. En su contra, son más vulnerables a factores de confusión.

Los estudios prospectivos piloto exploratorios, comparten con los ECA muchos aspectos, pero no están sujetos a la supervisión por parte de comisiones externas ni a la obligatoriedad de su registro. El *multitesting*, puede pervertir el balance de publicaciones a favor del efecto buscado. El razonamiento de Bonferroni muestra que, si se realizan 10 estudios con un antibiótico no efectivo, la probabilidad de que al menos uno arroje P <0,05 pude ser del 40%**.** Escenarios en los que hay mucha presión para investigar, como la reciente pandemia, son propicios para que muchos equipos traten de estudiar el efecto de un antimicrobiano. Aunque el fármaco no tenga ninguna eficacia, si 100 equipos de investigación realizan un estudio para valorar su utilidad, puede ser prácticamente seguro que aparecerá al menos uno con P <0,05. Si los demás estudios (con P >0,05) no se publican, la comunidad científica consideraría que hay fuerte evidencia a favor su la utilidad.

En conclusión, los ECA son una muy buena fuente de información clínica, pero no la única. El registro sistemático de todas las investigaciones iniciadas puede y debe aplicarse a todo tipo de estudios clínicos.

Palabras clave: metodología, estadística, ensayos clínicos.

INTRODUCTION

Clinical studies (with human beings) can be divided, simplistically, into observational and prospective interventional studies (Figure 1). Although there are situations where aspects of these categories overlap, this outline helps to clarify the advantages and disadvantages of each type of design.

In observational studies, the researcher does not perform any type of action on the subjects, and only observes the clinical situation, personal, and environmental circumstances, looking for possible relationships between conditions and risk or preventive factors. In prospective interventional studies, the physicians undertake an action on the subjects and observe the response that occurs in the short- or medium-term. For example, an antimicrobial is given to patients with an infection and its possible benefits and side effects are investigated. Two large categories of prospective interventional studies are distinguished: exploratory pilot studies and randomized clinical trials (RCTs) that, in addition, are controlled, blinded, and registered. RCTs are key to the advancement of medicine and microbiology. However, they are not the only possible option, but rather they share importance with other types of studies. In this article, we will try to show: 1) the error of disregarding all information not coming from RCTs, 2) that the different types of design do not compete with each other but rather are complementary, 3) the precautions to take when interpreting studies results.

OBSERVATIONAL/CASE-CONTROL STUDIES VS. PROSPECTIVE STUDIES

Observational studies can provide information on long-term efficacy and safety that is typically lacking in RCTs. In addition, they are less expensive, allow to study rare events and to obtain information more quickly. New and ongoing developments in data and analytics technology, such as artificial intelligence and big data, offer a promising future for these studies.

We should not question its usefulness, since many treatments and interventions aimed at preventing or solving health problems, with proven effectiveness, have not been subjected to rigorous evaluation using RCTs [1]. From the so-called evidence-based medicine, it is not correct to demand the adoption of interventions evaluated using only data from RCTs [2].

Observational studies include case reports and case series, ecological studies, cross-sectional studies, case-control (CC) studies, and cohort studies. The latter include clinical registries that are gaining increasing importance as a method to moni-

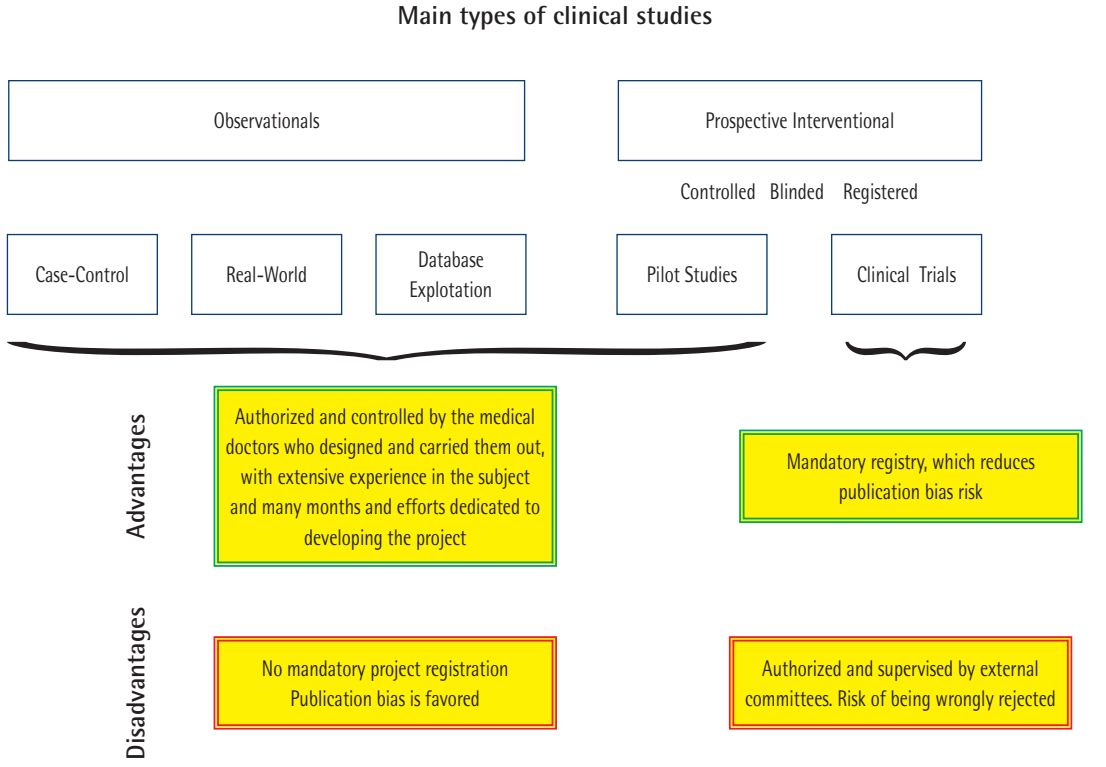

Figure 1 | **Most important types of clinical studies with their main advantages (in the green box) and disadvantages (in the red box).**

Table 1 Objectives, advantages, and disadvantages of observational studies.

Type of study	Aim	Advantages	Disadvantages
Case reports and case series	To describe new or extraordinary events	Easy, detailed information to generate hypotheses	No generalizable
Ecological studies	To describe data about a population	Easy if you use routinely collected data	No subject data
Cross-sectional studies	To describe population profiles or outcome of interest at a single point in time	Relatively easy	Absence of temporality
Case-control studies	To identify risk factors for an event or disease	You can explore rare events	Limited to a single event
Cohorts	To estimate the incidence of events and their determinants	Longitudinal. Study multiple events and risk factors	Relatively difficult, expensive and time-consuming

tor and improve the quality of healthcare [3]. The main types of observational studies used in health research, their purpose and main strengths and limitations are shown in Table 1. Its purpose may be descriptive, analytical or both [4]. Descriptive studies are designed primarily to describe the characteristics of a studied population while analytical studies seek to address questions of cause and effect or, at least, generate hypotheses in that sense [4].

Among the various types of observational studies, CC designs occupy a relevant place. A recent survey carried out among medical doctors attending a course on "Expansion of basic concepts of statistical analysis in medicine", carried out at the Chair of Statistical Analysis and Big Data of the Catholic University of Murcia, showed that more than 80% were not able to identify the difference between the term "*controlled*" applied to prospective studies and the noun "*control*" used to designate CC studies (unpublished data). Although the word is the same, in prospective studies the control group does not receive the treatment we are studying, while in CC design the control group does not have the disease we are studying.

CC studies take a random sample of patients with a certain disease and another random sample of people without that disease (healthy or with health problems not related to the condition). In both groups, the frequency of individuals who had been exposed to a certain factor will be evaluated. To be more specific, supposing that we ask ourselves if following a certain diet is associated with the frequency of meningitis. A prospective study would consist of taking a sample of, for example, 180 people, randomizing them into two groups, with and without that diet, following them for twenty years and comparing the percentage of meningitis that appears in each group. In the CC approach, we take a sample of 90 cases of meningitis and another of 90 people who have not suffered that infection and we find out the percentage of people who followed that diet during the last 20 years. We see that the CC approach requires much less time, because the 20 years that patients must be followed with the prospective design, in the CC "have already passed" when the research is done. Another advantage of CC designs is that, depending on how frequent meningitis is and the consumption of that diet, the statistical power can be much greater than with a prospective study. For instance, if 30% of people follow that diet and meningitis affects 1% of the population that does not use it and 4% of the population that uses it, (taking that diet multiplies the risk of suffering from the disease by 4), the statistical power of the study, for a P value of the test 0.05, is 0.92. The probability of finding a P value <0.05 is 0.92, that is, of every hundred studies that were carried out with this design, 92 would yield a P value <0.05. With a prospective study (RCT or pilot), the statistical power of the study, for a P value of the test 0.05, is 0.16. The probability of finding a P value <0.05 is 0.16, that is, of every hundred studies that were carried out with this design, only 16 would show a P value <0.05.

It must be considered that CC studies do not allow, in principle, to estimate relative risks (RR) that indicate how much greater the risk of disease is in patients on the diet than in those who do not follow it. CC studies allow us to estimate the odds ratio (OR), which is another way to quantify the harmful effect (in this example) of the diet. In this assumption it would be OR = 3.13, very close to the RR = 3. This proximity occurs whenever the risks involved are small, but with greater risks the value of the OR can be very different from the value of the RR. For instance, if the risk of a certain infection were 60% in those who follow the diet and 20% in those who do not follow it, the RR is 3, which tells us that following the diet multiplies the percentage of patients by 3. But, in this case, the OR is 6, which tells us that following the diet multiplies by 6 the number of sick people for every healthy person. With a CC study we could estimate this OR value, but not the RR value 3. Supplementary material depicts the concept of odd and OR.

Moreover, it must also be said that CC studies are much more vulnerable to the action of confounding factors. Part of this confusion is controlled with different types of multivariate analysis, regarding factors that have been recorded in each study. Another part can be controlled by sampling in a stratified and even paired manner. However, it will rarely be possible

to control as effectively as randomization does in prospective studies. In observational studies, adjustment for potential confounders can be performed and techniques such as propensity score, but only for a limited number of confounders and only those that are known and have been collected. Randomization in RCTs minimizes selection bias, while blinding controls information bias. Therefore, to, for example, know the effectiveness of a drug, RCTs provide the strongest evidence. However, this reality should not lead us to disregard the information provided by observational studies; information that is increasingly more precise and refined with new analysis methods. In fact, technological advances are changing the way in which observational studies are carried out [5].

NEW TECHNIQUES FOR ANALYSIS AND REPORT OF OBSERVATIONAL STUDIES

Even without randomizing subjects, methods have emerged in recent years that allow for less biased comparisons of two or more subgroups. Propensity score is a way of bringing together two or more groups for comparison, so that they appear to have been randomly assigned to an intervention or a comparator. In summary, the method involves logistic regression analysis to determine the probability (propensity) of each person within a cohort who was in the intervention, and then matching subjects who were in the intervention with those who were not, based on those propensity scores. The results are then compared between the two groups [6].

Increasing sophistication in data collection techniques, artificial intelligence, and the use of big data is also enabling continued improvements in the ability to conduct observational studies. Automatic linking of multiple data already offers a convenient way to capture results, even retrospectively. However, ethical considerations must be considered, such as whether informed consent may be required before data is linked, or who can access it. Machine learning already enables the capture, processing and analysis of unstructured text. New statistical techniques allow the imputation of missing data [7], a frequent problem in observational studies.

Unfortunately, the reporting of observational study research is often inadequate, making it difficult to evaluate their strengths and weaknesses and extrapolate results. The Strengthening The Reporting of OBservational studies In Epidemiology (STROBE) initiative [8] has allowed us to develop recommendations on how an observational study should be designed and reported. This initiative focuses on the three main types of observational studies: cohort, CC, and cross-sectional. It is based on a checklist with 22 items (the STROBE statement) that relate to the title, abstract, introduction, methods, results, and discussion sections of the articles. The vast majority of the items (18 of them) are common to the three types of study and four are specific for cohort, case-control or cross-sectional studies. STROBE is to observational studies what the Statement of Consolidated Standards of Reporting Trials (CONSORT) is for clinical trials. Both initiatives have helped improve the quality of studies and, above all, the way they are reported. Similar initiatives exist for other areas of research, for example, for reporting meta-analyses or diagnostic studies. In any case, STROBE is not a panacea nor does it free us from the biases and limitations inherent to observational studies. Yes, it is a useful tool that provides guidance on how to report the results of observational research correctly. Although these recommendations are not prescriptions for designing or conducting studies, they must be considered when planning any observational study. Furthermore, while clarity of reporting is a prerequisite for evaluation, the checklist is not an instrument for evaluating the quality of observational research. This means that an observational study that meets all the STROBE items may still have important gaps. The STROBE statement is a key checklist before writing a paper with the results of an observational study. Its sections include the title and summary of the article (item 1), the introduction (items 2 and 3), the methods (items 4 to 12), the results (items 13 to 17) and the discussion sections (items 18 to 17). 21), and other information (point 22 on financing).

PROSPECTIVE PILOT EXPLORATORY STUDIES

Prospective exploratory pilot studies, hereinafter "pilot", share many aspects with RCTs, but they differ from them in two important issues:

a) They are not subject to supervision, authorization, and possible veto by external commissions, in which the authors of the study do not participate.

b) There is no systematic record of each of them when it is launched, which is why it is much more difficult to have a record of studies with "negative" results. Therefore, it is practically impossible to avoid publication bias.

The advantages of submitting a research project to the supervision of an external commission are evident. If the external commission that evaluates a research project is made up of truly qualified professionals who can dedicate the necessary time to this evaluation, they would undoubtedly make observations that could improve the project. But here are three points that require detailed reflection:

I) Committees cannot include experts in all fields. Most likely, no member of the committee is an expert on the topic to be evaluated and, if there is one, he or she may not know the topic better than the researchers may. In cases where this commission decides to enlist the help of an expert in the field, that person will know the topic under study, but probably will not know it better than the parents of the project.

II) In general, the people who make up that commission – or the expert consulted – will be able to dedicate many fewer hours to the evaluation than those the authors dedicated to preparing it.

III) It is necessary to evaluate very carefully when it makes sense for the evaluation commission to reject a project. In this aspect, three types of situations must be distinguished: a) when the evaluation committee is a doctoral thesis committee or another academic degree, or has to decide if a project de-

serves financial aid, it is obvious that for each project it has to accept it or not; b) when the committee is the editorial board of a scientific journal, it must also accept it for publication or not; c) in other situations the evaluation commission does not perform these two functions. So, it is questionable whether that commission has the power to veto a project. There are frequent cases in which the objections made by these committees to justify their veto of a project are of a methodological nature (not of a clinical nature) and, upon closer inspection, turn out to be wrong. This error would not have major negative consequences if the rejection were advisory, because the authors, after verifying with an expert that the objection is wrong, would ignore it. However, if the objection implies a veto and appealing that "sentence" is difficult, the most common thing is that the authors of the project give up continuing with it and abandon an initiative that could have provided useful knowledge.

An argument frequently put forward is that these commissions ensure patient safety, defending their rights and - it is assumed - protecting them from possible abuse by researchers. However, there is little reason to think that the members of the external commission will take better care of patients than the doctors who are in personal and direct contact with them. Attending physicians do not ask any committee for authorization every morning to explore and treat each of their patients. For all these reasons, it does not seem appropriate for the evaluation committee to have veto power when this is not an essential part of their mission [9].

REGISTRATION OF MEDICAL STUDIES AND PUBLICATION BIAS

In principle, all RCTs that are launched are registered and their authors undertake to publish the results, since it is assumed – with good judgment – that, if the study is well planned and developed, its result, whatever it may be, provides useful information. However, in practice it is very difficult to get studies published that do not show some "statistically significant" effect. Even the most serious and honest authors when they find poor results tend to give the study as "failed", that is, it was not possible to carry it out properly, instead of "with a negative result" and assume that it is not necessary to publish their work. Thus, we have the problem of multitesting, which can seriously pervert the final balance of publications towards the desired effect. Bonferroni's reasoning helps us quantify the probabilities of finding results with a test P value lower than a certain limit, if several attempts are made and only those that yield a sufficiently small P value are considered worthy of publication.

Let us consider the case in which the pathogen "A", causing a serious infection with very high mortality, was sensitive to a certain antibiotic, but has recently developed resistance, resulting in a strain resistant to all currently known antibiotics. A study aimed at verifying whether it is sensitive to the new drug "B", that has given very promising "provisional" results, creates high expectations, which lead a large number of teams to carry out studies that can confirm it. A pertinent design would be to randomize 100 patients with this infection into two groups of 50, one with placebo and the other with "B". If the antibiotic is not effective, the study will most likely return a result with a relatively large P value, say greater than 0.05. But if several studies of the same type are carried out with ineffective drugs, the probability that at least one of them will yield a P value < 0.05 increases significantly with the number of studies carried out. Specifically, if N studies are performed, we have: probability (at least one study with P <0.05) = 1 - (1 - 0.05)^N.

Thus, if 10 studies are carried out with an ineffective antibiotic, the probability that at least one will show P < 0.05 is 1 - (1 - 0.05)^{10} = 1 - 0,95 ^{10} = 1 - 0,60 = 0,40**.** And if 40 studies are carried out, the probability that at least one shows P < 0.05 is 1 - 0.95^{40} = 0.83. There are scenarios in which there is a lot of pressure to research the treatment of an infection, the pandemic is possibly the best example. It is therefore plausible that the number of teams that decide to do this research reaches 100 and in this case the probability that at least one returns P <0.05 is 0.994, that is, with a useless drug, it is practically certain that it will appear at least one with P value <0.05. In fact, one study with P <0.01 and others around 4 studies with P <0.05 are very likely. If all other studies (with P >0.05) are not published, the scientific community would consider that there is strong evidence in favor of the usefulness of that drug. To quantify this evidence, a meta-analysis could be carried out with the five published ones and a P value < 0.001 would be obtained.

A possible resource to partially alleviate the problem of multitesting would be to ask for a smaller test P value, for example 0.01, to consider that there is sufficient evidence in favor of the new drug being effective. However, the accumulation of studies has an effect that is only partially counteracted by this lowering of the value that is set as a threshold. Applying the previous formula, we find that the probability that at least one study yields P < 0.01 is 0.10 for N = 10; 0.33 for N = 40 and 0.63 for N = 100. We see that the probability of finding studies with "significant" results when there is not really the desired effect is high and if the medical scientific community does not have access to studies with negative results that have appeared simultaneously with the positive ones, is committed to considering good products and procedures that are useless. In some cases, these treatments can even have a harmful effect, as we have seen in the case of hydroxychloroquine used for COVID-19 infection [10].

The problem of publication bias arises in the most general case, where there is no promising previous data regarding a specific product. It is enough that there is – as is usual in medicine – a problem to which a solution is sought and many research groups are mobilized for it. If each group tests a different product or procedure, the probability that one of them that is truly useless will be declared useful also increases according to the Bonferroni formula and therefore the need to faithfully report all clinical studies that are launched. It is imperative to reduce publication bias.

RCTs have this component – the systematic recording of all studies initiated – that is very positive, but it is obvious that the same praxis can be applied to all types of clinical studies. The entire administrative infrastructure that enables the registration of RCTs can and should accommodate the registration of prospective, pilot and exploratory clinical studies. The logistics involved are complicated and expensive, but the medical science community has no choice. If there are no rigorous systematic prior records that allow us to know at least a good part of the studies with negative results, the publication bias is very high. Only with these records and the publication of negative results is it possible to carry out reliable meta-analyses.

In conclusion, RCTs are a very good source of clinical information, but not the only one. The systematic registration of all research initiated can and should be applied to all types of clinical studies.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Yeh RW, Valsdottir LR, Yeh MW, Shen C, Kramer DB, Strom JB, et al; PARACHUTE Investigators. Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial. BMJ. 2018;363:k5094. doi: 10.1136/bmj.k5094. Erratum in: BMJ. 2018 Dec 18;363:k5343.
2. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. Int J Prosthodont. 2006;19(2):126-8.
3. Gilmartin-Thomas JF, Liew D, Hopper I. Observational studies and their utility for practice. Aust Prescr. 2018;41(3):82-85. doi: 10.18773/austprescr.2018.017.
4. Diamond GA. Randomized trials, observational registries, and the foundations of evidence-based medicine. Am J Cardiol. 2014;113(8):1436-41. doi:10.1016/j.amjcard.2014.01.420.
5. Ricotta EE, Rid A, Cohen IG, Evans NG. Observational studies must be reformed before the next pandemic. Nat Med. 2023;29(8):1903-1905. doi: 10.1038/s41591-023-02375-8.
6. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. Clin Ther. 2007;29 Spec No:1284-92.
7. Mainzer R, Moreno-Betancur M, Nguyen C, Simpson J, Carlin J, Lee K. Handling of missing data with multiple imputation in observational studies that address causal questions: protocol for a scoping review. BMJ Open. 2023;13(2):e065576. doi:10.1136/bmjopen-2022-065576.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7. doi: 10.1016/S0140-6736(07)61602-X. PMID: 18064739.
9. Carazo Díaz C, Prieto L, Martínez-Sellés M. Errores y malentendidos que entorpecen la investigación médica y dificultan el avance de la medicina. REC Interv Cardiol. 2024 (in press). DOI: https://doi.org/10.24875/RECIC.M23000436
10. Pradelle A, Mainbourg S, Provencher S, Massy E, Grenet G, Lega JC. Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate. Biomed Pharmacother. 2024;171:116055. doi: 10.1016/j.biopha.2023.116055.

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Review

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Iván Sanz-Muñoz[1,2,3]
Laura Sánchez-de Prada[1]
Javier Castrodeza-Sanz[1,4]
José M Eiros[1,3,5,6]

Microbiological and epidemiological features of respiratory syncytial virus

[1]National Influenza Centre, Valladolid, Spain
[2]Instituto de Estudios de Ciencias de la Salud de Castilla y León, ICSCYL, Soria, Spain
[3]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFECC), Spain
[4]Preventive Medicine and Public Health Unit, Hospital Clínico Universitario de Valladolid, Spain
[5]Microbiology Unit, Hospital Universitario Río Hortega, Valladolid, Spain
[6]Microbiology Unit, Hospital Clínico Universitario de Valladolid, Spain

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ABSTRACT

The properties of the main surface proteins and the viral cycle of the respiratory syncytial virus (RSV) make it an attractive pathogen from the perspective of microbiology. The virus gets its name from the manner it infects cells, which enables it to produce syncytia, which allow the virus' genetic material to move across cells without having to release viral offspring to the cellular exterior, reducing immune system identification. This causes a disease with a high impact in both children and adults over 60, which has sparked the development of several preventive interventions based on vaccines and monoclonal antibodies for both age groups. The epidemiological characteristics of this virus, which circulates in epidemics throughout the coldest months of the year and exhibits a marked genetic and antigenic drift due to its high mutation capability, must be taken into consideration while using these preventive methods. The most important microbiological and epidemiological elements of RSV are covered in this study, along with how they have affected the creation of preventive medications and their use in the future.

Keywords: Respiratory syncytial virus; F protein; microbiology; epidemiology

Características microbiológicas y epidemiológicas del virus respiratorio sincitial

RESUMEN

Las características de las principales proteínas de superficie y el ciclo vírico del virus respiratorio sincitial (VRS) lo convierten en un patógeno atractivo desde el punto de vista de la microbiología. El virus debe su nombre a la forma en que infecta las células, lo que le permite producir sincicios, que permiten que el material genético del virus se desplace a través de las células sin tener que liberar descendientes virales al exterior celular, lo que reduce la identificación por parte del sistema inmunitario. Esto provoca una enfermedad con un alto impacto tanto en niños como en adultos mayores de 60 años, lo que ha motivado el desarrollo de diversas intervenciones preventivas basadas en vacunas y anticuerpos monoclonales para ambos grupos de edad. Las características epidemiológicas de este virus, que circula en epidemias durante los meses más fríos del año y presenta una marcada deriva genética y antigénica debido a su alta capacidad de mutación, deben ser tenidas en cuenta a la hora de utilizar y diseñar estos métodos preventivos. En esta revisión se abordan los elementos microbiológicos y epidemiológicos más importantes del VRS, así como la forma en que han afectado a la creación de medicamentos preventivos y a su uso en el futuro.

Palabras clave: Virus respiratorio sincitial; proteína F; microbiología; epidemiología

INTRODUCTION

After COVID-19 pandemic, there has been a surge of interest in virology, particularly in microbes that have a significant impact on human health but have previously gone unnoticed. One of these is respiratory syncytial virus (RSV), which generates annual epidemics primarily in infants but also has a significant influence on the elderly's health.

Before pandemic, multiple product concepts for RSV prevention in various age groups were in development. Among the prophylactic approaches available were monoclonal antibodies for passive immunization and vaccinations for children and people >60 years. This, combined with the inclusion of this virus in most surveillance systems globally, particularly in Europe, illustrates the high level of interest in this pathogen and the burden of disease it causes.

Correspondence:
Dr. Iván Sanz-Muñoz
National Influenza Centre, Valladolid, Spain
Calle Rondilla de Santa Teresa s/n, Edificio Rondilla, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
E-mail: isanzm@saludcastillayleon.es

It is vital to have quality knowledge on the microbiological features of RSV, as well as the aspects involved in its seasonality and form of circulation, in order to understand the details of their use and the reasons for their use. As a result, we propose this narrative review focused on the virological features and an examination of the available RSV epidemiology data.

VIROLOGICAL FEATURES OF RSV

History of their discovery. RSV was first described in 1956 [1], but it was not until much later that it was linked to the respiratory disease it produces in humans [2]. In fact, the virus was discovered in a group of 14 chimps suffering from the common cold, and a virus was isolated from them that the researchers termed CCA, or "Chimpanze Coryza Agent" [3,4]. Antibodies were found in all convalescent animals, implying that the attack rate was 100% [5]. Furthermore, one of the animal caregivers had an acute respiratory infection and a detectable antibody response to this novel virus, but unlike the animals, the etiologic agent could not be identified in the respiratory samples. The pathogenicity of the CCA virus was demonstrated by re-inoculating the isolated virus in healthy chimps, who acquired the sickness three days later.

Subsequently, it was revealed that this same infectious agent caused respiratory illness in children, and that many of them had neutralizing antibodies against it, therefore the virus was named Respiratory Syncytial Virus [2] owing to the behavior it displayed in cell cultures. As 80% of 4-year-olds had antibodies against RSV, this led to the conclusion that CCA was a human virus that infrequently affected other primates [6]. The researchers Chanock and Finberg [6] found two distinct viruses in respiratory samples from children with bronchopneumonia and laryngotracheobronchitis, designating them "Long strain" and "Snyder strain," respectively. When it was discovered that the Long strain, as well as the Snyder and CCA strains, exhibited a very similar respiratory pathology, they were merged into a single group, Respiratory Syncytial Virus, as further papers describing this disease arose.

Classification and virological features of RSV. RSV is a virus belonging to the genus *Orthopneumovirus*, family *Pneumoviridae*, order Mononegavirales [7,8], and their species denomination is *Human orthopneumovirus* or *Orthopneumovirus hominis*. This family contains RSV as well as other viruses that affect various animals, such as bovine and murine RSV [7,9–11]. The other genus in the family *Pneumoviridae* that affects also human being is *Metapneumovirus*, which has only one representative, the human Metapneumovirus (hMPV) [2], which was initially reported in the Netherlands in 2001 [12].

RSV has a dual morphology, sometimes spherical with a diameter of roughly 100-350 nm and occasionally filamentous with a diameter of 60-200 nm [13]. In reality, when cultivated in cells, its filamentous form is common, with many of the virions remaining attached to the infected cell and not being released until certain procedures are used.

The genetic material is made up of single-stranded, unsegmented, negatively polarized RNA [14], which is made up of 15,000 nucleotides. The RSV genome is organized into 10 genes and 11 ORFs (Open Reading Frames) encoding 11 structural and non-structural proteins, NS1, NS2, N, P, M, SH, G, F, M2-1 & M2-2 (encoded by two ORFs) and L [15,16] (Figure 1) (Table 1). The genetic material is surrounded by many proteins, includ-

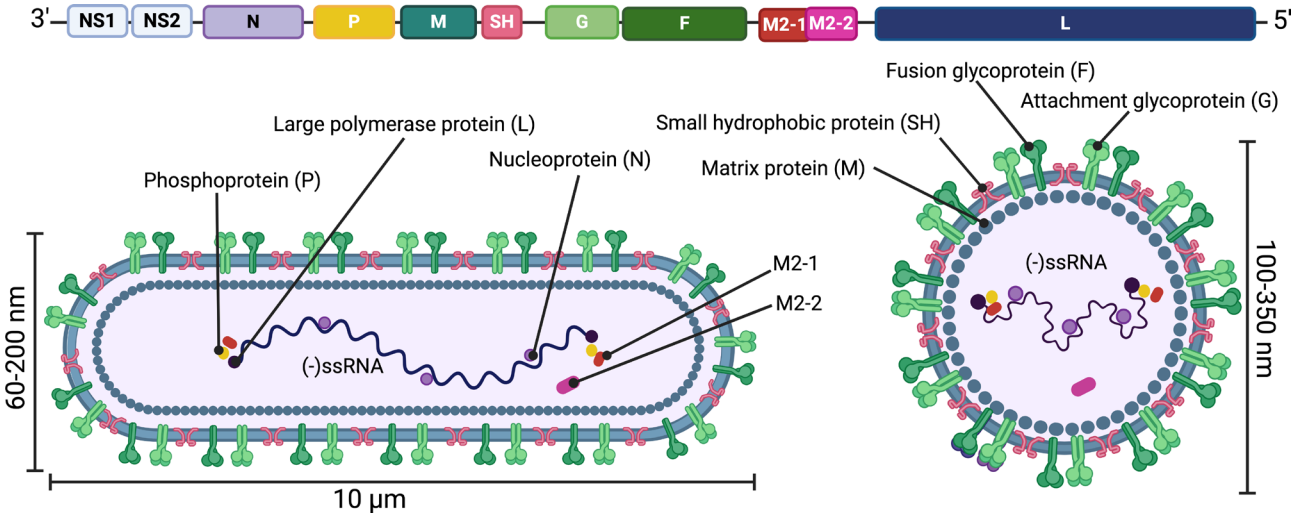

Figure 1 Morphological features of the Respiratory Syncytial Virus and genomic organization and structure of genes. On the left site, filamentous form and on the right site spherical form. M2-1 and M2-2 are represented inside the virion but are not present in nature because they are non-structural proteins. M2-1 and M2-2 genes are overlapped because they pertain to the same gene but are translated by different ORFs (Open Reading Frames). Created with BioRender.com.

Tabla 1 **Features of the genes and proteins composing the RSV genome. Modified from Collins *et al.* [17].**

Protein	Length nucleotides	Length aminoacids	Type	Location	Function
G	923	298	Structural	Lipid envelope	Attachment
F	1903	574	Structural	Lipid envelope	Fusion/attachment
SH	410	64	Structural	Lipid envelope	Viroporin/ion channel
M	958	256	Structural	Inner envelope face	Assembly
N	1203	391	Structural	Ribonucleocapsid	RNA-binding
P	914	241	Structural	Ribonucleocapsid	Phosphoprotein
L	6578	2165	Structural	Ribonucleocapsid	Polymerase
M2-1	961	194	Nonstructural	Ribonucleocapsid	Transcription processivity factor
M2-2	961	90	Nonstructural	Not present in virion	Transcription RNA replication
NS1	532	139	Nonstructural	Not present in virion	Inhibit type I IFN induction and signaling, inhibit apoptosis
NS2	503	124	Nonstructural	Not present in virion	Inhibit type I IFN induction and signaling, inhibit apoptosis

ing nucleoprotein (N), phosphoprotein (P), and RNA-dependent polymerase (L), which are involved in the encapsulation of the virion RNA to create the ribonucleoprotein (RNP) complex, which is part of the viral replication machinery. Furthermore, M2-1 and M2-2 proteins proceed from the same gene expressing two different proteins by two different ORFs. M2-1 protein is an enzyme that increases RNA transcription processivity, and M2-2 has regulatory activities in RNA replication and transcription [17]. The M, or matrix protein, is found beneath the virus membrane and is in charge of viral structural integrity, as well as mechanisms associated to virion production and virus outward "budding."

RSV contains three distinct membrane glycoproteins. Protein G is a cell adhesion protein with the primary function of anchoring to the host cell membrane. The F protein is involved in the fusion of the cytoplasmic membrane of the host cell and the viral membrane. The SH (Short Hydrophobic) protein generates an ion channel that is required for virion internalization into the cell. RSV contains two extra proteins that are not found in other paramyxoviruses. These are the non-structural NS1 and NS2 proteins, which have roles linked to interferon production inhibition, cell signaling limiting, and apoptosis inhibition [17].

To protect themselves from enzymatic destruction, to be recognized by cellular translation mechanisms [18], and to escape identification by certain immune system elements [19], the mRNAs that give rise to these proteins are methylated at the 5' end and have polyA tails at the 3' end. Except for the M2 gene, which has two separate ORFs producing M2-1 and M2-2 proteins, the genetic material is arranged from 3' to 5', and each gene expresses its matching mRNA. The genome starts at 3' with an extragenic area of 44 nucleotides before the NS1 gene and ends with another extragenic region of 155 nucleotides after the L gene. The first nine genes are separated by a brief spacer of 1-58 nucleotides that has no known function and varies between virus genotypes.

Functions of G, F and SH proteins. Antigenic sites and their importance for disease prevention. RSV surface glycoproteins G and F are the most important. These two proteins are responsible for virus adherence to the host cell and virion internalization within the cell, and therefore for the virus's infectious process.

Protein G is an approximately 80 kDa heavily glycosylated protein. Depending on the serotype, it has approximately 298 amino acids. It has so many carbohydrate groups connected to the protein that the glycosylated portion accounts for 60% of the total protein weight [20]. Its primary purpose is to keep RSV attached to the host cell. The action of this protein is known from trials in which RSV adherence to HeLa cells was reduced using specific antibodies against the G protein, demonstrating that the function of this protein was cell adhesion [21]. However, this protein serves other purposes. It plays a role in both the inflammatory response and immunological evasion. G protein may mimic some cellular receptors and be responsible for some inhibitory effects, such as those caused by TNF-α [22]. As a result, future vaccines directed against this immunogenic protein should help to minimize illness by lowering virus-induced inflammation as well as viral replication [23,24].

The F protein (fusion protein) is a 574-amino acid transmembrane protein [25]. It is synthesized in its inactive state (F0) and is surrounded by strain-dependent glycans. F protein is made up of three F0 monomers (trimer). This inactive protein is cleaved by furin-like proteases [26], resulting in the formation of two protein subunits, F1 and F2, which are covalently connected by disulfide bridges [27], activating the F protein to its post-fusion state [20]. The hydrophobic fusion peptide is buried in a central cavity of the protein in the pre-fusion state

(F0), and the protein undergoes a conformational change that results in a new folding of the protein that allows insertion of the fusion peptide into the host cell membrane by a currently unknown mechanism [28]. This permits the viral and host cell membranes to gradually approach each other [29], resulting in membrane fusion and internalization of the virion and its genetic material for starting of the viral replication cycle. Specific antibodies against the F protein have been found to impede membrane fusion and thereby prevent infection and its severity [30]. Furthermore, some researchers believe that the F protein can facilitate cell adhesion and fusion in the absence of G and SH proteins, making it one of the most important targets for vaccination [31].

The F protein's membrane-fusion function is responsible not only for virion internalization but also for syncytium formation, which is characteristic of RSV disease and pathogenesis. During the viral replication cycle, the F protein is produced in infected cells and subsequently localized in the cell membrane, where it binds to other neighboring cells and causes them to fuse [32]. As a result, syncytia form, which are multicellular and multinucleated formations without continuity dissolution, allowing the passage of the virus's genetic material from one cell to another without the need to leave the cell [33], favoring transmission and avoiding, at some extent, immune system activity. This pathway is required for RSV pathogenesis and cytotoxicity. This syncytium-forming impact is also seen in other viral diseases such as measles [34], HIV, herpes simplex virus, and, in rare circumstances, SARS-CoV-2 [35,36].

The virus interacts with the host cell via a variety of receptors. The G protein, for example, binds to CX3CR1 and HSPG (heparan sulfate proteoglycans) receptors, whereas the F protein interacts with nucleolin receptors, EGFR (Epidermal growth factor), IGF1R (Insulin-like growth factor-1 receptor), and ICAM-1 (Intercellular molecular adhesion-1) [14,20].

Finally, the SH protein is an integral membrane protein of 64-65 amino acids that is very phylogenetically conserved [37]. The SH protein acts as an ion channel to permeabilize the membrane of the infected cell. It is also involved in the prevention of apoptosis in infected cells.

Evolution/mutation rate. Genetic variability, viral evolution, immune escape and impact on reinfections. RSV is formed by two distinct subtypes, A and B, that differ fundamentally by antigenic and genetic drift of the virus, which happens mostly through the G protein but also in the other viral proteins at less extent [10]. These two subtypes were initially described based on reactivity to monoclonal antibodies [38], but it was later discovered that the differences between them were more complex, and were based, as previously noted, on the existing variety in the sequence of their different genes. There are several genotypes within subtypes A and B in this sense, but there is no agreement on their nomenclature and characterization [39,40]. In fact, this evolutionary process, which involves the introduction of new genotypes into populations where others were previously circulating and the extinction of the latter [40], is very similar to the seasonal dynamics of other respiratory viruses such as influenza and, more recently, SARS-CoV-2, which involves the continuous emergence of new variants, the introduction of the same and new populations, and the extinction of the previous ones [41].

RSV's mutation rate, like that of other RNA viruses, is significant, resulting in constant genetic and antigenic drift with repercussions for humans. RSV, like influenza viruses, is very variable, and the lack of a proof-reading exonuclease (which exists in SARS-CoV-2) results in a mutation rate of roughly $10^{-3}/10^{-4}$ nucleotide substitutions/site/year [41–44], depending on the gene and strain. RSV-A viruses appear to have a lower mutation rate ($1.48x10^{-3}$ nucleotide substitutions/site/year) than RSV-B viruses ($1.92x10^{-3}$ nucleotide substitutions/site/year) [41]. This high mutation rate results in the continuous selection of new strains or variants as a result of immune system pressure, among other mechanisms [39], which has a clear impact on the medium/long term development of effective vaccines, antivirals, and monoclonal antibody treatments [1].

The aforementioned genetic and antigenic diversity resulted in a full genotype classification [45,46]. RSV-A has 9 genotypes (GA1-GA7, SAA1 and NA1) [1], but RSV-B has at least 32 genotypes (BA1-14, GB1-GB5, SAB1-4, URU1-2, NZB1-2, BA-CCA, BA-CCB, BA-C, CBB and CB1) [41]. These distinct genotypes of both groups can co-circulate in the same RSV season in consecutive years, but the predominant genotype often changes each year [47]. This rapid divergence and evolution is a problem for vaccines in development or near to be approved, since they must create a broad response against all genotypes while maintaining a distinct response against each genotype.

Within the two RSV proteins with the highest antigenic capability (G and F), the G protein exhibits a 10-fold stronger antigenic drift than F and other internal virus genes [48]. RSV-A viruses (NA1 genotype) have a 72-nucleotide duplication in the G protein, while RSV-B viruses (BA genotype) have a 60-nucleotide duplication [1]. These duplications in the G protein's genetic material have resulted in an increase in viral fitness, causing these two genotypes to spread fast around the world [49]. The F protein, on the other hand, is far more conserved, thus while both proteins are of relevance for vaccine and monoclonal antibody creation, the F protein has a greater interest since it may have higher long-term utility. Nonetheless, there are genetic and antigenic changes in the F protein (particularly in RSV-B viruses), so its genetic drift will have to be taken into account in the future for the adaptation of these preventive treatments, as is done with influenza viruses and will most likely be done with SARS-CoV-2 infections.

The immune system's pressure is substantially responsible for RSV's genetic and antigenic drift [39]. The high variability of the G protein indicates positive selection, allowing the virus immune escape to the host, whereas the lower variability of other proteins, including F, indicates that they are genes that specialize and optimize over time and have important functions in the cell cycle related to genetic material replication and viral transmission.

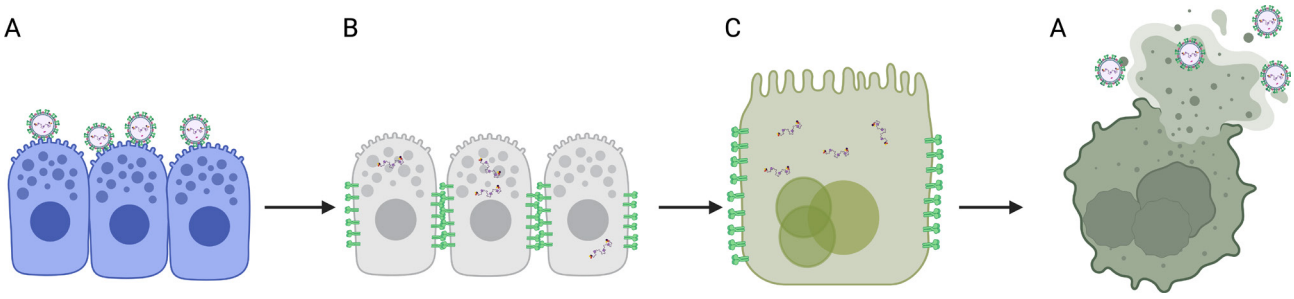

Figure 2 **Mechanism of infection and syncytia formation of respiratory syncytial virus. First the virus attach to the cell through G protein (A) and insert their genetic material after fusion of viral/cell membranes via activation of F protein. After that, the genetic material starts their replication and mRNA translation for protein formation. The F protein is then produced and located into the cell host membrane (B), attaching the infected cell to the next one and forming syncytia (C), a superstructure formed by several cells with only one cytoplasm but with several nuclei, where the genetic material of the virus can travel from one cell to another. When the virus produces damage into the syncytia, this triggers the death of several cells at the same time. Created with BioRender.com.**

Other processes, like as recombination, which can generate new genotypes, allow the virus to evolve. According to some authors, these recombination can only occur between genotypes of the same group (A or B), not between groups [41]. However, there is limited data indicating co-infections of many genotypes in the same individual, which could allow for this form of recombination, thus further research is needed in this area. Despite this, the recombination hypothesis may be realistic because other viruses, such as SARS-CoV-2, have experienced this effect, such as the development of the XBB variation as a result of BA.2.10.1 and BA.2.75 recombination [50].

The aforementioned RSV variability, mediated by the aforementioned processes, results in recurrent reinfections. According to certain research, 36-42% of children suffered RSV reinfections within their first five years of life [51]. RSV infections do not elicit a long-lasting immune response, but reinfections are typically milder than the original episode [52]. Antibodies produced during the first infection do not vanish, but the antibody titer tends to diminish over time, resulting in the recurrence of similar episodes, albeit with reduced clinical signs. One of the most critical determinants in reinfection is age, particularly for reinfections that occur during the same RSV season in which the kid was first infected. These reinfections are more common and severe in younger children [53].

Viral cycle. RSV infection characteristics are greatly depending on cell type. When RSV enters the respiratory system by inhalation, it attaches via the G protein to the ciliated cells of the respiratory epithelium via the receptors indicated above, most notably CX3CR1. Following this interaction, the F protein is activated in its post-fusion state and the virion binds to the host cell membrane, fusing both membranes and initiating internalization [17]. The virion nucleocapsid is then released into the cell cytoplasm, where the viral genome, along with the N protein, forms a helical structure and associates with the polymerase-RNA-dependent complex. The polymerase then starts transcribing viral mRNAs and replicating the genome, generating positive polarity RNA sequences (antigenome) that serve as a template for the synthesis of negative polarity RNA that will be part of the viral offspring [54]. The "de novo" synthesized genomes bind to the structural proteins that comprise the polymerase-RNA-dependent complex and the N protein to form new nucleocapsids, which are then transported to the infected cell's plasma membrane to bind to the rest of the structural proteins and produce the new virions that are released from the infected cell.

Pathogenic effect of the virus through the creation of syncytia. Although the virus can continue its infectious cycle by releasing virions into the extracellular space, the formation of syncytia is another prevalent method of intercellular transmission in RSV, which also lends the virus its name. As previously stated, syncytia are cellular clusters that share the same area within a single lipid membrane but contain several cell nuclei. This superstructure permits viral genetic material to be transported between cells without being released into the cellular space, resulting in a very efficient transmission system that also hides the virus from immune system action [55] (Figure 2).

One implication of syncytia formation is that the peak viral load occurs later than in other viral infections that do not induce syncytia [56,57]. Another difference is that this type of virus progression appears to be a viral evasion strategy, with a direct impact on the severity of infection [55]. Another implication of syncytium formation is that, unlike in the case of an influenza infection, where cell death occurs one at a time, cell death occurs abruptly in the case of RSV and syncytia, in which many cells die at the same time because they are part of the same syncytium, which has been dubbed the "burst model" [58]. This huge cell death appears to be linked to significant lung injury, which has a direct impact on the progression of

the disease and consequently the severity of the clinical process [59]. Although syncytia development impacts other disorders, such as COVID-19, the exact processes by which it worsens the condition in these patients remain unknown.

Antigenic sites in the F protein and the possible impact on vaccine effectiveness and protection. Six distinct antigenic regions in the F protein have been identified as being of particular significance for the production of vaccines and monoclonal antibodies. These antigenic sites were discovered both before and after fusion. Neutralizing antibodies were developed in the following sequence of potency: site Ø, site V, site III, site IV, site II, and site I [60]. Sites Ø and V are exclusively present in the F protein's pre-fusion conformation, but the others are present in both, with considerable differences in the effectiveness of neutralizing antibodies produced against them (up to 80-fold in some circumstances) [60].

Given that the Ø and V sites are the most potent inducers of neutralizing antibodies, and that these are only present in the pre-fusion state of the protein, the great majority of vaccine and monoclonal antibody designs will target the pre-fusion form of this protein. Sixty percent of the neutralizing antibodies found against the F protein target the Ø and V sites. The most likely explanation for these large differences is that the Ø and V sites on the F protein are much more topologically accessible than the rest, in addition to the angle of approach of the antibodies, which interacts with other annexin structures less than other antigenic sites on the same protein [61].

In terms of the technique to be taken to avoid infection or minimize its severity, the two preventative strategies available at present time are drastically different. Vaccines formulated against the F protein in its pre-fusion condition generate a broad polyclonal antibody response when manufactured using the complete protein. In other words, antibodies are made preferentially towards the most accessible antigenic sites Ø and V, although antibodies against other sections of the protein are also formed [62]. However, antibody treatments such as nirsevimab and palivizumab are directed against specific epitopes (in the case of nirsevimab Ø and II in the case of palivizumab) [63], implying that we are dealing with monoclonal antibodies [64]. This results in significant discrepancies in active and passive immunization techniques, despite the fact that both paradigms examine different areas of protection and are, of course, complementary.

Several Spanish hospitals conducted the first global estimate of nirsevimab's effectiveness using real-world evidence, which was published in February 2024 [65]. According to this trial, in infants under 9 months old who were candidates for this vaccine, nirsevimab was found to be effective in preventing laboratory-confirmed RSV LRTI (low-respiratory tract infections) by 70% to 84%, with coverages exceeding 90%.

EPIDEMIOLOGICAL FEATURES OF THE RSV

Features of the transmission of RSV. RSV is transmitted by infected people's secretions via the respiratory pathway [66]. Furthermore, children with bronchiolitis produce aerosols that might transport the virus via extremely small droplets that are easily spread [67]. On the other hand, other authors suggest that aerosol transmission is inefficient, since investigations in pediatric primary care found that just 2.3% of aerosol samples collected had detectable RSV [68]. As a result, the process of respiratory transmission necessitates, above all, closeness between two people. Furthermore, some authors argue that fomite contamination may be an additional pathway for virus transmission [69], albeit of lesser consequence than respiratory transmission. RSV has a basic reproductive number of roughly 3.0 (SD=0.6) [65]. However, as with all respiratory diseases, this number varies based on the features of the individual source of infection (behavior, age, etc.), as well as the preventive measures implemented throughout the virus's circulation months.

This fast transmission rate has an impact on more than just the process by which the virus spreads from an infected individual to a vulnerable one. Other elements, like as coexistence and interpersonal interactions, also have a role. The characteristics of families and persons living together in the family setting are highly linked to RSV transmission. Some authors, for example, show that infections in younger children frequently develop when the virus enters the home via an older sibling's infection [70,71]. Younger children who are not in school have a very restricted contact regimen, but older children who are already in day care/school are more likely to become infected, developing a milder condition but having a significant influence on younger children who are cohabitants due to their age. Children, on the other hand, can transmit RSV to older caregivers, which can be harmful if they have risk diseases [72,73]. Vaccination measures for older children may thus be beneficial in preventing sickness in younger children.

Features of epidemic circulation and lasting of epidemics. During the coldest months of the year, RSV spreads like wildfire. It is typically diagnosed in the northern hemisphere between the months of October and March, with the epidemic peak recorded in several European nations around week 48-50 of the year, about at the end of December [68,69] (Figure 3). Epidemics in these countries last from 12-32 weeks, depending on the territory and the characteristics of the surveillance system (a total of 5-6 months). RSV epidemics often spread from the southern hemisphere to the northern hemisphere. They begin in the southern hemisphere in March and June and conclude in the northern hemisphere in September and December [74,75]. However, in tropical climatic areas, the RSV season might last up to ten months [76].

The seasonal prevalence of RSV in temperate regions may reflect one of two previously proposed ideas for influenza viruses. The first theory holds that epidemics during the cold months of the year are caused by new virus introductions from countries with widespread virus circulation, either from the opposite hemisphere or from tropical or subtropical climates where the virus adopts a type of endemic circulation [78]. These reintroductions would occur on a regular basis,

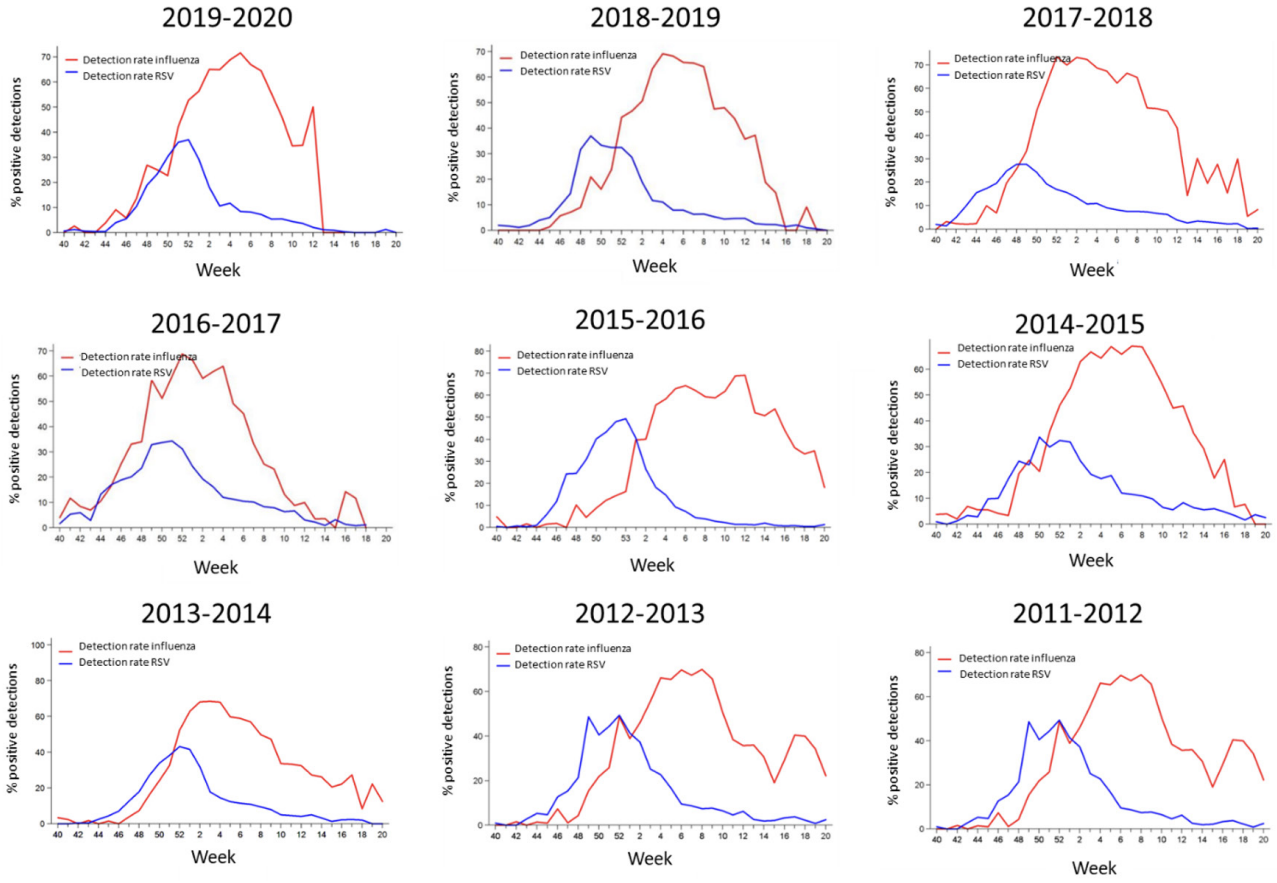

Figure 3 | **Circulation of RSV and influenza viruses during the last 9 epidemic seasons before the COVID-19 pandemic in Spain. Modified from Instituto de Salud Carlos III [77].**

but in unfavorable times due to an unfavorable climate for the virus in temperate climes, brief chains of transmission would occur, which would not result in epidemics. On the contrary, once the cold months arrive and the above-mentioned environmental conditions (low temperatures, low absolute humidity, overcrowding, etc.) favor virus persistence, reintroductions from other parts of the world lead to longer chains of transmission, eventually leading to epidemics, as seen with influenza [79].

Alternatively, the second hypothesis proposes that the virus will remain dormant in select populations, such as immunocompromised persons such as HIV/AIDS patients and even children, until the following season [40]. These people are generally long-term virus excretors, even weeks or months [80,81], since they are unable to clear the infection or reduce the viral load, but they are often asymptomatic or pauci-symptomatic. However, until the appearance of COVID-19, current surveillance systems focused their efforts on influenza and exclusively on the epidemiological surveillance period (week 40 of one year to week 20 of the following year), making it difficult to discover this sort of case.

For example, in the case of influenza, one of the most widely accepted explanations for the annual occurrence of epidemics is that reintroductions are the primary driver of this seasonality. Indeed, the "East-Southeast Asian epicenter model" hypothesis, proposed by Smith *et al.* in 2008, demonstrated the existence of a continuous reservoir of influenza in East and Southeast Asia, which could be the epicenter of strains that were then distributed globally in each epidemic, both in the northern and southern hemispheres [82]. These scientists even claimed that dispersions out of this part of the world had little effect on the evolutionary divergence of influenza viruses, implying that this epicenter was responsible for the majority of the virus's antigenic alterations. Similar patterns have been seen by other researchers from several tropical climatic reservoirs [78]. However, as previously discussed, the possibility that RSV could survive for a long time in non-immunocompromised populations should not be discounted. According to some authors, the mixed hypothesis is the most correct. Indeed, due to nitric oxide activity, RSV may remain latent in monocyte-derived dendritic cells for lengthy periods of time [83,84], which could be significant to the occurrence of epidemics or non-periodic seasonal outbreaks in temperate regions.

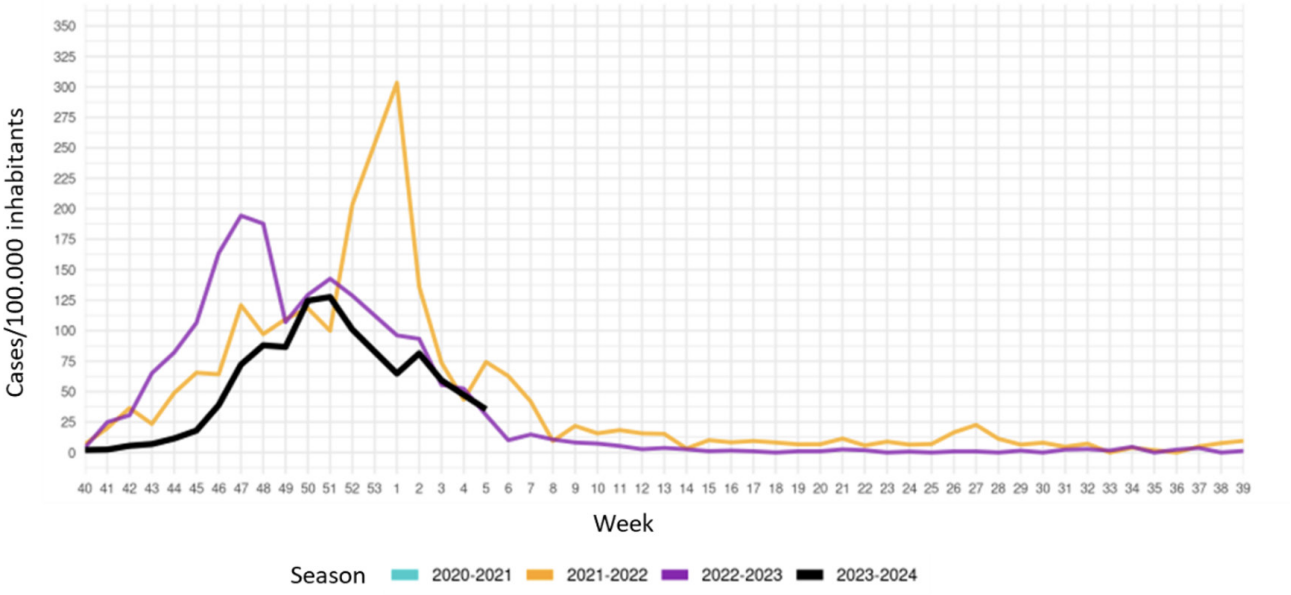

Figure 4 | **Incidence rate (cases/100.000 inhabitants) of RSV in Spain during the last five seasons since the emergence of COVID-19 pandemic. Modified from SIVIRA [96].**

RSV has been described as having two subtypes (RSV-A and RSV-B) and various genotypes, as previously stated. Historical divergence statistics indicate that the two RSV groups may have separated in the year 1681 [41]. The two RSV subtypes frequently co-circulate in the same epidemic [38,85], however one subtype predominates over the other depending on the year [86]. Which subtype is more widespread is highly dependent on the season, the affected population, the territory, and the people's immunological background. However, numerous reports claim that subtype A is more common than subtype B in around 60% of outbreaks [87,88]. Both RSV subtypes have similar pathologic characteristics in illness manifestation. However, there appears to be a larger prevalence of ICU hospitalizations in pediatric RSV-A patients than in RSV-B patients [89].

Impact of the COVID-19 pandemic on the RSV circulation. The COVID-19 pandemic changed the way all respiratory viruses behaved. Mask use, social isolation, travel bans to other countries, and isolation all abruptly halted the spread of SARS-CoV-2 and other respiratory-transmitted viruses [90]. However, the relaxation of these measures beginning in 2021 caused some respiratory viruses to partially resurface, albeit with epidemiological characteristics in terms of timing of presentation that were not normal compared to before the pandemic (higher intensity, longer months of circulation, localization of epidemics in unusual months of the year, and so on).

In Japan, for example, the 2021 RSV outbreak began in July, significantly earlier than usual [91]. This was due not only to the relaxation of the aforementioned measures, but also to the fact that many countries adopted strict measures to keep children away from the virus, closing daycare centers, schools, and even parks to prevent transmission [88], effectively keeping them in a bubble in which only adults were responsible for the virus's entry into the home environment. In 2021, an unseasonalized RSV outbreak occurred in France as well, beginning in February and lasting until about May of that year [92]. Pinquier *et al.* found a 3-4 month disparity between what happens in this country and what happens in other countries. Other studies have found similar shifts in various countries, primarily during the off-season and notably in late RSV epidemics [93].

RSV behavior in 2022 was more similar to that observed prior to the pandemic, with the virus emerging in several nations in the fall months, albeit significantly earlier. The majority of cases (91%) in the United States were caused by different genotypes of the RSV-A subtype. This revival was severe, with detection and hospitalization rates higher than before the pandemic [94]. Other countries, such as Spain, have also reported a more severe RSV outbreak in 2022 compared to previous years, particularly among younger children [95]. The national reports produced by the SiVIRA tool (ARI Surveillance System) at the state level demonstrate this anomalous behavior. They indicate a delocalized epidemic peak in comparison to other post COVID-19 epidemics, with the epidemic peak occurring in week 1/2023, and a very high incidence, approaching 300 cases/100,000 inhabitants [96]. Following that, both the incidence and the pattern that accompanied the epidemic peak in the 2023–2024 season were comparable to those of prior years (Figure 4).

CONCLUSIONS

RSV has a significant influence on human health, particu-

larly in youngsters and the elderly. The virological and genetic properties of this virus constitute a barrier for the development of appropriate preventative strategies to avoid the disease from a microbiological standpoint. Among these obstacles is the high variability of the G protein, which is primarily responsible for reinfections in the initial years of life, as well as an etiopathogenesis of the disease that inhibits the immune system's ability to eradicate the virus. However, the characteristics of the RSV F protein in the prefusion state have made viable the appearance of different preventive treatments, which have already seen or will see the light of day in the coming years.

It is desirable to improve existing knowledge on the epidemiological realities of RSV, particularly the disease's influence on human health, not only in infants but also in older age groups. This may allow us to assess who will gain the most from the advent of this sort of preventative medicine, allowing us to prioritize its usage in these populations. Robust surveillance mechanisms, in addition to those already in place for influenza and COVID-19, are required to properly track the virus's activities. The breakthroughs in RSV treatment and prevention that are now being achieved will likely allow for progress in many aspects of its treatment and prevention during the coming decade.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Muñoz-Escalante JC, Comas-García A, Bernal-Silva S, Robles-Espinoza CD, Gómez-Leal G, Noyola DE. Respiratory syncytial virus A genotype classification based on systematic intergenotypic and intragenotypic sequence analysis. Sci Rep 2019;9:20097. https://doi.org/10.1038/s41598-019-56552-2.
2. Walsh EE, Hall CB. Respiratory Syncytial Virus (RSV). Mand Douglas Bennetts Princ Pract Infect Dis 2015:1948-1960.e3. https://doi.org/10.1016/B978-1-4557-4801-3.00160-0.
3. Blount RE, Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med Soc Exp Biol Med N Y N 1956;92:544–9. https://doi.org/10.3181/00379727-92-22538.
4. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999;282:1440–6. https://doi.org/10.1001/jama.282.15.1440.
5. Caroline B Hall, Edward E Walsh. Respiratory Syncytial Virus. Feigin Cherrys Textb. Pediatr. Infect. Dis., vol. 3, 2012. https://doi.org/10.1016/B978-1-4557-4801-3.00160-0.
6. Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. Am J Hyg 1957;66:281–90. https://doi.org/10.1093/oxfordjournals.aje.a119901.
7. ICTV. Virus taxonomy. The ICTV Report on virus classification and taxon nomenclature. Pneumoviridae Chapter. 2017 cited on 11th of December 2023.. Available: http://taxonomy.cvr.gla.ac.uk/PDF/Pneumoviridae.pdf
8. Susana Payne. Family Pneumoviridae. En: Viruses From understanding to investigation. 2.ª ed. Elsevier; 2023. p. 233-7.
9. Hao M, Li Y, Wang Y, Zhang S. A Classification Study of Respiratory Syncytial Virus (RSV) Inhibitors by Variable Selection with Random Forest. Int J Mol Sci 2011;12:1259–80. https://doi.org/10.3390/ijms12021259.
10. WHO. Respiratory Syncytial Virus (RSV) disease. 2023 cited on 11th of December 2023. Available: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/respiratory-syncytial-virus-disease
11. ICTV. Family: Pneumoviridae 2023.
12. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24. https://doi.org/10.1038/89098.
13. Jeffree CE, Rixon HWM, Brown G, Aitken J, Sugrue RJ. Distribution of the attachment (G) glycoprotein and GM1 within the envelope of mature respiratory syncytial virus filaments revealed using field emission scanning electron microscopy. Virology 2003;306:254–67. https://doi.org/10.1016/s0042-6822(02)00016-8.
14. Feng Z, Xu L, Xie Z. Receptors for Respiratory Syncytial Virus Infection and Host Factors Regulating the Life Cycle of Respiratory Syncytial Virus. Front Cell Infect Microbiol 2022;12:858629. https://doi.org/10.3389/fcimb.2022.858629.
15. McNamara PS, Smyth RL. The pathogenesis of respiratory syncytial virus disease in childhood. Br Med Bull 2002;61:13–28. https://doi.org/10.1093/bmb/61.1.13.
16. Huang YT, Collins PL, Wertz GW. Characterization of the 10 proteins of human respiratory syncytial virus: identification of a fourth envelope-associated protein. Virus Res 1985;2:157–73. https://doi.org/10.1016/0168-1702(85)90246-1.
17. Collins PL, Fearns R, Graham BS. Respiratory Syncytial Virus: Virology, Reverse Genetics, and Pathogenesis of Disease. Curr Top Microbiol Immunol 2013;372:3–38. https://doi.org/10.1007/978-3-642-38919-1_1.
18. Lodish HF, Rose JK. Relative importance of 7-methylguanosine in ribosome binding and translation of vesicular stomatitis virus mRNA in wheat germ and reticulocyte cell-free systems. J Biol Chem 1977;252:1181–8.
19. Hyde JL, Diamond MS. Innate immune restriction and antagonism of viral RNA lacking 2′-O methylation. Virology 2015;479–480:66–74. https://doi.org/10.1016/j.virol.2015.01.019.
20. McLellan JS, Ray WC, Peeples ME. Structure and Function of RSV Surface Glycoproteins. Curr Top Microbiol Immunol 2013;372:83–104. https://doi.org/10.1007/978-3-642-38919-1_4.

21. Levine S, Klaiber-Franco R, Paradiso PR. Demonstration that glycoprotein G is the attachment protein of respiratory syncytial virus. J Gen Virol 1987;68 (Pt 9):2521–4. https://doi.org/10.1099/0022-1317-68-9-2521.
22. Langedijk JP, de Groot BL, Berendsen HJ, van Oirschot JT. Structural homology of the central conserved region of the attachment protein G of respiratory syncytial virus with the fourth subdomain of 55-kDa tumor necrosis factor receptor. Virology 1998;243:293–302. https://doi.org/10.1006/viro.1998.9066.
23. Miao C, Radu GU, Caidi H, Tripp RA, Anderson LJ, Haynes LM. Treatment with respiratory syncytial virus G glycoprotein monoclonal antibody or F(ab')2 components mediates reduced pulmonary inflammation in mice. J Gen Virol 2009;90:1119–23. https://doi.org/10.1099/vir.0.009308-0.
24. Tripp RA, Power UF, Openshaw PJM, Kauvar LM. Respiratory Syncytial Virus: Targeting the G Protein Provides a New Approach for an Old Problem. J Virol 2018;92:e01302-17. https://doi.org/10.1128/JVI.01302-17.
25. Collins PL, Huang YT, Wertz GW. Nucleotide sequence of the gene encoding the fusion (F) glycoprotein of human respiratory syncytial virus. Proc Natl Acad Sci U S A 1984;81:7683–7.
26. Bolt G, Pedersen LO, Birkeslund HH. Cleavage of the respiratory syncytial virus fusion protein is required for its surface expression: role of furin. Virus Res 2000;68:25–33. https://doi.org/10.1016/s0168-1702(00)00149-0.
27. Day ND, Branigan PJ, Liu C, Gutshall LL, Luo J, Melero JA, et al. Contribution of cysteine residues in the extracellular domain of the F protein of human respiratory syncytial virus to its function. Virol J 2006;3:34. https://doi.org/10.1186/1743-422X-3-34.
28. McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, et al. Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody. Science 2013;340:1113–7. https://doi.org/10.1126/science.1234914.
29. McLellan JS, Yang Y, Graham BS, Kwong PD. Structure of respiratory syncytial virus fusion glycoprotein in the postfusion conformation reveals preservation of neutralizing epitopes. J Virol 2011;85:7788–96. https://doi.org/10.1128/JVI.00555-11.
30. Swanson KA, Settembre EC, Shaw CA, Dey AK, Rappuoli R, Mandl CW, et al. Structural basis for immunization with postfusion respiratory syncytial virus fusion F glycoprotein (RSV F) to elicit high neutralizing antibody titers. Proc Natl Acad Sci U S A 2011;108:9619–24. https://doi.org/10.1073/pnas.1106536108.
31. Techaarpornkul S, Barretto N, Peeples ME. Functional Analysis of Recombinant Respiratory Syncytial Virus Deletion Mutants Lacking the Small Hydrophobic and/or Attachment Glycoprotein Gene. J Virol 2001;75:6825–34. https://doi.org/10.1128/JVI.75.15.6825-6834.2001.
32. König P, Giesow K, Schuldt K, Buchholz UJ, Keil GM. A novel protein expression strategy using recombinant bovine respiratory syncytial virus (BRSV): modifications of the peptide sequence between the two furin cleavage sites of the BRSV fusion protein yield secreted proteins, but affect processing and function of the BRSV fusion protein. J Gen Virol 2004;85:1815–24. https://doi.org/10.1099/vir.0.80010-0.
33. Domachowske JB, Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. Clin Microbiol Rev 1999;12:298–309. https://doi.org/10.1128/CMR.12.2.298.
34. Herschke F, Plumet S, Duhen T, Azocar O, Druelle J, Laine D, et al. Cell-Cell Fusion Induced by Measles Virus Amplifies the Type I Interferon Response. J Virol 2007;81:12859–71. https://doi.org/10.1128/JVI.00078-07.
35. Lin L, Li Q, Wang Y, Shi Y. Syncytia formation during SARS-CoV-2 lung infection: a disastrous unity to eliminate lymphocytes. Cell Death Differ 2021;28:2019–21. https://doi.org/10.1038/s41418-021-00795-y.
36. Leroy H, Han M, Woottum M, Bracq L, Bouchet J, Xie M, et al. Virus-Mediated Cell-Cell Fusion. Int J Mol Sci 2020;21:9644. https://doi.org/10.3390/ijms21249644.
37. Gan S-W, Tan E, Lin X, Yu D, Wang J, Tan GM-Y, et al. The Small Hydrophobic Protein of the Human Respiratory Syncytial Virus Forms Pentameric Ion Channels. J Biol Chem 2012;287:24671–89. https://doi.org/10.1074/jbc.M111.332791.
38. Mufson MA, Örvell C, Rafnar B, Norrby E. Two Distinct Subtypes of Human Respiratory Syncytial Virus. J Gen Virol 1985;66:2111–24. https://doi.org/10.1099/0022-1317-66-10-2111.
39. Trento A, Ábrego L, Rodriguez-Fernandez R, González-Sánchez MI, González-Martínez F, Delfraro A, et al. Conservation of G-Protein Epitopes in Respiratory Syncytial Virus (Group A) Despite Broad Genetic Diversity: Is Antibody Selection Involved in Virus Evolution? J Virol 2015;89:7776–85. https://doi.org/10.1128/JVI.00467-15.
40. Agoti CN, Otieno JR, Ngama M, Mwihuri AG, Medley GF, Cane PA, et al. Successive Respiratory Syncytial Virus Epidemics in Local Populations Arise from Multiple Variant Introductions, Providing Insights into Virus Persistence. J Virol 2015;89:11630–42. https://doi.org/10.1128/JVI.01972-15.
41. Yu J-M, Fu Y-H, Peng X-L, Zheng Y-P, He J-S. Genetic diversity and molecular evolution of human respiratory syncytial virus A and B. Sci Rep 2021;11:12941. https://doi.org/10.1038/s41598-021-92435-1.
42. Haider MSH, Khan WH, Deeba F, Ali S, Ahmed A, Naqvi IH, et al. BA9 lineage of respiratory syncytial virus from across the globe and its evolutionary dynamics. PloS One 2018;13:e0193525. https://doi.org/10.1371/journal.pone.0193525.
43. Zlateva KT, Lemey P, Vandamme A-M, Van Ranst M. Molecular evolution and circulation patterns of human respiratory syncytial virus subgroup a: positively selected sites in the attachment g glycoprotein. J Virol 2004;78:4675–83. https://doi.org/10.1128/jvi.78.9.4675-4683.2004.
44. Pandya MC, Callahan SM, Savchenko KG, Stobart CC. A Contemporary View of Respiratory Syncytial Virus (RSV) Biology and Strain-Specific Differences. Pathogens 2019;8:67. https://doi.org/10.3390/pathogens8020067.
45. Salimi V, Viegas M, Trento A, Agoti CN, Anderson LJ, Avadhanula V, et al. Proposal for Human Respiratory Syncytial Virus Nomenclature below the Species Level. Emerg Infect Dis 2021;27:e204608.

https://doi.org/10.3201/eid2706.204608.

46. Goya S, Galiano M, Nauwelaers I, Trento A, Openshaw PJ, Mistchenko AS, et al. Toward unified molecular surveillance of RSV: A proposal for genotype definition. Influenza Other Respir Viruses 2020;14:274–85. https://doi.org/10.1111/irv.12715.
47. Peret TC, Hall CB, Schnabel KC, Golub JA, Anderson LJ. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. J Gen Virol 1998;79 (Pt 9):2221–9. https://doi.org/10.1099/0022-1317-79-9-2221.
48. Tan L, Lemey P, Houspie L, Viveen MC, Jansen NJG, van Loon AM, et al. Genetic variability among complete human respiratory syncytial virus subgroup A genomes: bridging molecular evolutionary dynamics and epidemiology. PloS One 2012;7:e51439. https://doi.org/10.1371/journal.pone.0051439.
49. Bin Lu, Liu H, Tabor DE, Tovchigrechko A, Qi Y, Ruzin A, et al. Emergence of new antigenic epitopes in the glycoproteins of human respiratory syncytial virus collected from a US surveillance study, 2015–17. Sci Rep 2019;9:3898. https://doi.org/10.1038/s41598-019-40387-y.
50. Scarpa F, Sanna D, Azzena I, Casu M, Cossu P, Fiori PL, et al. Genome-based comparison between the recombinant SARS-CoV-2 XBB and its parental lineages. J Med Virol 2023;95:e28625. https://doi.org/10.1002/jmv.28625.
51. Bont L, Versteegh J, Swelsen WTN, Heijnen CJ, Kavelaars A, Brus F, et al. Natural reinfection with respiratory syncytial virus does not boost virus-specific T-cell immunity. Pediatr Res 2002;52:363–7. https://doi.org/10.1203/00006450-200209000-00009.
52. Henderson FW, Collier AM, Clyde WA, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med 1979;300:530–4. https://doi.org/10.1056/NEJM197903083001004.
53. Winterstein AG, Hampp C, Saidi A. Effectiveness of palivizumab prophylaxis in infants and children in Florida. Pharmacoepidemiol Drug Saf 2012;21:53–60. https://doi.org/10.1002/pds.2246.
54. Collins PL, Huang YT, Wertz GW. Identification of a tenth mRNA of respiratory syncytial virus and assignment of polypeptides to the 10 viral genes. J Virol 1984;49:572–8. https://doi.org/10.1128/JVI.49.2.572-578.1984.
55. Cifuentes-Muñoz N, Ellis Dutch R. To assemble or not to assemble: The changing rules of pneumovirus transmission. Virus Res 2019;265:68–73. https://doi.org/10.1016/j.virusres.2019.03.002.
56. Jessie B, Dobrovolny HM. The role of syncytia during viral infections. J Theor Biol 2021;525:110749. https://doi.org/10.1016/j.jtbi.2021.110749.
57. Gonzàlez-Parra G, De Ridder F, Huntjens D, Roymans D, Ispas G, Dobrovolny HM. A comparison of RSV and influenza in vitro kinetic parameters reveals differences in infecting time. PLoS ONE 2018;13:e0192645. https://doi.org/10.1371/journal.pone.0192645.
58. Chen HY, Di Mascio M, Perelson AS, Ho DD, Zhang L. Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques. Proc Natl Acad Sci U S A 2007;104:19079–84. https://doi.org/10.1073/pnas.0707449104.
59. Buchrieser J, Dufloo J, Hubert M, Monel B, Planas D, Rajah MM, et al. Syncytia formation by SARS-CoV-2-infected cells. EMBO J 2020;39:e106267. https://doi.org/10.15252/embj.2020106267.
60. Taleb SA, Al Thani AA, Al Ansari K, Yassine HM. Human respiratory syncytial virus: pathogenesis, immune responses, and current vaccine approaches. Eur J Clin Microbiol Infect Dis 2018;37:1817–27. https://doi.org/10.1007/s10096-018-3289-4.
61. Gilman MSA, Castellanos CA, Chen M, Ngwuta JO, Goodwin E, Moin SM, et al. Rapid profiling of RSV antibody repertoires from the memory B cells of naturally infected adult donors. Sci Immunol 2016;1:eaaj1879. https://doi.org/10.1126/sciimmunol.aaj1879.
62. Mukhamedova M, Wrapp D, Shen C-H, Gilman MSA, Ruckwardt TJ, Schramm CA, et al. Vaccination with prefusion-stabilized respiratory syncytial virus fusion protein induces genetically and antigenically diverse antibody responses. Immunity 2021;54:769-780.e6. https://doi.org/10.1016/j.immuni.2021.03.004.
63. Ye X, Iwuchukwu OP, Avadhanula V, Aideyan LO, McBride TJ, Ferlic-Stark LL, et al. Antigenic Site-Specific Competitive Antibody Responses to the Fusion Protein of Respiratory Syncytial Virus Were Associated With Viral Clearance in Hematopoietic Cell Transplantation Adults. Front Immunol 2019;10:706. https://doi.org/10.3389/fimmu.2019.00706.
64. Pantaleo G, Correia B, Fenwick C, Joo VS, Perez L. Antibodies to combat viral infections: development strategies and progress. Nat Rev Drug Discov 2022;21:676–96. https://doi.org/10.1038/s41573-022-00495-3.
65. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, López-Labrador FX, Mengual-Chuliá B, Fernández-García C, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Eurosurveillance 2024;29:2400046. https://doi.org/10.2807/1560-7917.ES.2024.29.6.2400046.
66. Kulkarni H, Smith C, Hirst R, Baker N, Easton A, O'Callaghan C. Airborne transmission of respiratory syncytial virus (RSV) infection. Eur Respir J 2011;38. https://doi.org/10.1126/science.abd9149
67. Kulkarni H, Smith CM, Lee DDH, Hirst RA, Easton AJ, O'Callaghan C. Evidence of Respiratory Syncytial Virus Spread by Aerosol. Time to Revisit Infection Control Strategies? Am J Respir Crit Care Med 2016;194:308–16. https://doi.org/10.1164/rccm.201509-1833OC.
68. Grayson SA, Griffiths PS, Perez MK, Piedimonte G. Detection of airborne respiratory syncytial virus in a pediatric acute care clinic. Pediatr Pulmonol 2017;52:684–8. https://doi.org/10.1002/ppul.23630.
69. Hall CB, Douglas RG, Geiman JM. Possible transmission by fomites of respiratory syncytial virus. J Infect Dis 1980;141:98–102. https://doi.org/10.1093/infdis/141.1.98.
70. Colosia AD, Masaquel A, Hall CB, Barrett AM, Mahadevia PJ, Yogev R. Residential crowding and severe respiratory syncytial virus disease among infants and young children: A systematic literature review. BMC Infect Dis 2012;12:95. https://doi.org/10.1186/1471-2334-12-95.
71. Heikkinen T, Valkonen H, Waris M, Ruuskanen O. Transmission of Respiratory Syncytial Virus Infection Within Families. Open Forum Infect Dis 2014;2:ofu118. https://doi.org/10.1093/ofid/ofu118.

72. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. Thorax 2019;74:986–93. https://doi.org/10.1136/thoraxjnl-2018-212212.

73. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;352:1749–59. https://doi.org/10.1056/NEJMoa043951.

74. Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PloS One 2013;8:e54445. https://doi.org/10.1371/journal.pone.0054445.

75. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003;22:S21-32. https://doi.org/10.1097/01.inf.0000053882.70365.c9.

76. Robertson SE, Roca A, Alonso P, Simoes EAF, Kartasasmita CB, Olaleye DO, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 2004;82:914–22.

77. Instituto de Salud Carlos III (ISCIII). Sistema de vigilancia de la gripe en España 2020 cited 16th of May 2023.. Available: https://vgripe.isciii.es/inicio.do

78. Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature 2008;453:615–9. https://doi.org/10.1038/nature06945.

79. Lowen A, Palese P. Transmission of influenza virus in temperate zones is predominantly by aerosol, in the tropics by contact. PLoS Curr 2009;1:RRN1002. https://doi.org/10.1371/currents.RRN1002.

80. Munywoki PK, Koech DC, Agoti CN, Kibirige N, Kipkoech J, Cane PA, et al. Influence of age, severity of infection, and co-infection on the duration of respiratory syncytial virus (RSV) shedding. Epidemiol Infect 2015;143:804–12. https://doi.org/10.1017/S0950268814001393.

81. Madhi SA, Venter M, Madhi A, Petersen MK, Klugman KP. Differing manifestations of respiratory syncytial virus-associated severe lower respiratory tract infections in human immunodeficiency virus type 1-infected and uninfected children. Pediatr Infect Dis J 2001;20:164–70. https://doi.org/10.1097/00006454-200102000-00010.

82. Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, et al. The global circulation of seasonal influenza A (H3N2) viruses. Science 2008;320:340–6. https://doi.org/10.1126/science.1154137.

83. Hobson L, Everard ML. Persistent of respiratory syncytial virus in human dendritic cells and influence of nitric oxide. Clin Exp Immunol 2008;151:359–66. https://doi.org/10.1111/j.1365-2249.2007.03560.x.

84. Martinón-Torres F, González-Barcala F-J. Where does Respiratory Syncytial Virus Hide? Arch Bronconeumol 2022;58:T298–9. https://doi.org/10.1016/j.arbres.2021.06.022.

85. Johnson PR, Spriggs MK, Olmsted RA, Collins PL. The G glycoprotein of human respiratory syncytial viruses of subgroups A and B: extensive sequence divergence between antigenically related proteins. Proc Natl Acad Sci U S A 1987;84:5625–9. https://doi.org/10.1073/pnas.84.16.5625.

86. Mufson MA, Belshe RB, Orvell C, Norrby E. Respiratory syncytial virus epidemics: variable dominance of subgroups A and B strains among children, 1981-1986. J Infect Dis 1988;157:143–8. https://doi.org/10.1093/infdis/157.1.143.

87. Ciarlitto C, Vittucci AC, Antilici L, Concato C, Di Camillo C, Zangari P, et al. Respiratory Syncityal Virus A and B: three bronchiolitis seasons in a third level hospital in Italy. Ital J Pediatr 2019;45:115. https://doi.org/10.1186/s13052-019-0704-0.

88. Song J, Zhu Z, Song J, Mao N, Cui A, Xu W, et al. Circulation pattern and genetic variation of human respiratory syncytial virus in China during 2008–2021. J Med Virol 2023;95:e28611. https://doi.org/10.1002/jmv.28611.

89. Laham FR, Mansbach JM, Piedra PA, Hasegawa K, Sullivan AF, Espinola JA, et al. Clinical Profiles of Respiratory Syncytial Virus Subtypes A and B among Children Hospitalized with Bronchiolitis. Pediatr Infect Dis J 2017;36:808–10. https://doi.org/10.1097/INF.0000000000001596.

90. Sanz-Muñoz I, Tamames-Gómez S, Castrodeza-Sanz J, Eiros-Bouza JM, de Lejarazu-Leonardo RO. Social Distancing, Lockdown and the Wide Use of Mask; A Magic Solution or a Double-Edged Sword for Respiratory Viruses Epidemiology? Vaccines 2021;9:595. https://doi.org/10.3390/vaccines9060595.

91. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan. Emerg Infect Dis 2021;27:2969–70. https://doi.org/10.3201/eid2711.211565.

92. Pinquier D, Crépey P, Tissières P, Vabret A, Roze J-C, Dubos F, et al. Preventing Respiratory Syncytial Virus in Children in France: A Narrative Review of the Importance of a Reinforced Partnership Between Parents, Healthcare Professionals, and Public Health Authorities. Infect Dis Ther 2023;12:317–32. https://doi.org/10.1007/s40121-022-00737-2.

93. Chuang Y-C, Lin K-P, Wang L-A, Yeh T-K, Liu P-Y. The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus Infection: A Narrative Review. Infect Drug Resist 2023;16:661–75. https://doi.org/10.2147/IDR.S396434.

94. Adams G, Moreno GK, Petros BA, Uddin R, Levine Z, Kotzen B, et al. The 2022 RSV surge was driven by multiple viral lineages. medRxiv 2023:2023.01.04.23284195. https://doi.org/10.1101/2023.01.04.23284195.

95. IISCIII. Vigilancia centinela de Infección Respiratoria Aguda en Atención Primaria (IRAs) y en Hospitales (IRAG) Gripe, COVID-19 y otros virus respiratorios. Semana 14/2023. 2023 cited 14th of April 2023.. Available: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/GRIPE/Informes%20semanales/Temporada_2022-23/Informe%20semanal_SiVIRA_142023.pdf

96. SIVIRA, ISCIII. Vigilancia centinela de Infección Respiratoria Aguda en Atención Primaria (IRAs) y en Hospitales (IRAG): Gripe, COVID-19 y VRS CNE-CNM. ISCIII. Informe nº 168. Semana 05/2024 (del 29 de enero al 4 de febrero del 2024) 2024. cited 9th of February 2024] Available: https://docsivira.isciii.es/Informe_semanal_SiVIRA_202405_n168.html

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Review

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Cristóbal M Rodríguez-Leal[1]
Carlos González-Corralejo[2]
Francisco Javier Candel[3]
Miguel Salavert[4]
on behalf of collaborative authors and Medical societies for the 5th edition of Pneumonia Day (addenda)

Candent issues in pneumonia. Reflections from the Fifth Annual Meeting of Spanish Experts 2023

[1]Emergency Medicine Service. Hospital Universitario del Henares. Coslada (Madrid) Spain. SEMES.
[2]Clinical Microbiology Service. Hospital Universitario Clínico San Carlos. IdISSC & IML Health Research Institutes. Madrid. Spain. SEIMC.
[3]Francisco Javier Candel. Clinical Microbiology Service. Hospital Universitario Clínico San Carlos. IdISSC & IML Health Research Institutes. Madrid. Spain. GEIPC-SEIMC. INFURGSEMES-SEMES.
[4]Miguel Salavert. Infectious Diseases Service. Hospital Universitario y Politecnico la Fe. Valencia. Spain. GEIPC-SEIMC.

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ABSTRACT

Pneumonia is a multifaceted illness with a wide range of clinical manifestations, degree of severity and multiple potential causing microorganisms. Despite the intensive research of recent decades, community-acquired pneumonia remains the third-highest cause of mortality in developed countries and the first due to infections; and hospital-acquired pneumonia is the main cause of death from nosocomial infection in critically ill patients. Guidelines for management of this disease are available worldwide, but there are questions which generate controversy, and the latest advances make it difficult to stay them up to date. A multidisciplinary approach can overcome these limitations and can also aid to improve clinical results. Spanish medical societies involved in diagnosis and treatment of pneumonia have made a collaborative effort to actualize and integrate last expertise about this infection. The aim of this paper is to reflect this knowledge, communicated in Fifth Pneumonia Day in Spain. It reviews the most important questions about this disorder, such as microbiological diagnosis, advances in antibiotic and sequential therapy, management of beta-lactam allergic patient, preventive measures, management of unusual or multi-resistant microorganisms and adjuvant or advanced therapies in Intensive Care Unit.

Keywords: Community-acquired pneumonia, aetiology, management, therapeutic failure, nosocomial pneumonia, healthcare-associated pneumonia, epidemiology, diagnosis stewardship, prevention.

Correspondence
Francisco Javier Candel
Clinical Microbiology Service. Hospital Clínico San Carlos.
IdISSC and IML Health Research Institutes. 28040 Madrid. Spain.
E-mail: fj.candel@gmail.com. GEIPC-SEIMC, INFURGSEMES-SEMES

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Cuestiones candentes en neumonía. Reflexiones desde la V Reunión Anual de Expertos Españoles 2023

RESUMEN

La neumonía es una enfermedad polifacética con una amplia gama de manifestaciones clínicas, niveles de gravedad y microorganismos causantes potenciales. A pesar de la intensa investigación de las últimas décadas, la neumonía adquirida en la comunidad sigue siendo la tercera causa de mortalidad en los países desarrollados y la primera debida a infección; y la neumonía adquirida en el hospital es la principal causa de muerte por infección nosocomial en pacientes críticos. En todo el mundo existen directrices para el manejo de esta enfermedad, pero hay cuestiones que generan controversia y los últimos avances dificultan su actualización. Un enfoque multidisciplinar puede superar estas limitaciones y ayudar a mejorar los resultados clínicos. Varias sociedades médicas españolas implicadas en el diagnóstico y tratamiento de la neumonía han realizado un esfuerzo colaborativo para actualizar e integrar los últimos conocimientos sobre esta infección. El objetivo de este trabajo es reflejar estos conocimientos, comunicados en el V Día de la Neumonía en España. En él se revisan las cuestiones más importantes sobre este trastorno, como el diagnóstico microbiológico, los avances en la terapia antibiótica y secuencial, el manejo del paciente alérgico a betalactámicos, las medidas preventivas, el manejo de microorganismos inusuales o multirresistentes y las terapias coadyuvantes o avanzadas en la Unidad de Cuidados Intensivos.

Palabras clave. Neumonía adquirida en la comunidad, etiología, manejo, fracaso terapéutico, neumonía nosocomial, neumonía asociada a la asistencia sanitaria, epidemiología, diagnóstico, administración, prevención.

INTRODUCTION

Community-acquired pneumonia (CAP) is the infection with the higher mortality in industrialized countries. Not taking account COVID-19 (coronavirus disease 2019), it has an incidence of 1.2 cases per 1000 adults in Europe and 2.4 in USA. Higher rate of pneumococcal vaccination in Europe is believed to cause this difference. At extreme ages (under 5 and over 70-year-old) the incidence increases [1]. Hospital-acquired pneumonia (HAP) is also an important cause of morbidity, decreased quality of life, increased sanitary spending and mortality [2–6]. HAP is a pulmonary inflammatory process of infectious origin that develops after more than 48 hours from hospital admission time, was not previously incubating and was absent at time of admission. Ventilator-associated pneumonia (VAP) is a significant sub-set of HAP that appears in patients with an artificial airway more than 48-72 hours after tracheal intubation [7–9]. HAP is the main cause of death from nosocomial infection in critically ill patients (with an incidence of 5 to 10 cases per 1000 hospital admissions), while VAP affects 10-25% of all patients in intensive care units (ICU), with a higher mortality than HAP: 20-30% vs 20-50% respectively [10, 11].

Despite international guidelines implemented in all health systems, there is variability in the diagnostic and therapeutic management of these entities. Moreover, morbidity and mortality remain high and a multiprofessional approach is necessary to improve these rates [12, 13]. Finally, new information from clinical trials and epidemiological studies arises regularly so frequent actualization of knowledge is necessary.

Since 2019, an annual meeting of Pneumonia has been held by main Medical Societies involved in diagnosis and treatment of this disease in Spain. The fifth meeting happened on 14 November 2023 [14]. Experts of different medical specialities related to CAP, HAP and VAP presented the latest advances in their respective fields of action. The aim of the present paper is to synthesize the main ideas of each presentation showed in the meeting regarding the scientific program.

MATERIAL AND METHODS

Design. The Study Group of Infection in the Critically Ill Patient of the Spanish Society of Infectious Diseases and Clinical Microbiology (GEIPC-SEIMC) called experts of different Spanish Medical Societies involved in diagnosis and treatment of CAP, HAP, and VAP (listed in this document's affiliation) to make a narrative review of their respective field of knowledge and to present their conclusions in different workshops in the Annual Meeting of Pneumonia.

Search strategy. Between July and November 2023, the experts performed a bibliographic search of their corresponding topics in PubMed ((http://www.ncbi.nlm.nih.gov/pubmed/, accessed on 1 November 2023), Embase (http://www.elsevier.com/online-tools/embase/ , accessed on 1 November 2023) and Scopus (http://www.elsevier.com/onlinetools/scopus , accessed on 1 November 2023). They chose the most relevant and current articles in their opinion for each issue, to prepare a presentation of 45 minutes for the meeting.

Drafting. On 14 November 2023, two medical writers (CMRL and CGC) attended and then, between November and December, they wrote a text with the main ideas exposed in the meeting.

Revision. Between January and February of 2024, all the experts had the opportunity to read the complete text and raise objections and changes.

RESULTS

Microbiological diagnosis. Targeted treatment has always been a great challenge in planning clinical work algorithms for infectious diseases, especially in sepsis with respiratory origin or HAP/VAP [8]. The time elapsed from the start of empirical antibiotics to the selection of targeted treatment in intensive care units (ICUs) is marked mainly by the microbiological results obtained. This time is conditioned by clinical identification of infection, obtention of specimens for microbiological testing and laboratory processing of samples. Clinicians initiate empirical treatment, which becomes targeted treatment when microbiological results are available. That empirical treatment can be appropriate or inappropriate, so microbiological results can be used to maintain the same therapy, deescalate therapy or to escalate spectrum based on identification and susceptibility testing [15].

Due to the potential appearance of resistant bacteria and possible therapeutic failures associated with an incorrect choice of antibiotic, the microbiological diagnostic techniques have evolved mainly in two aspects: response time and kind of information provided. Molecular biology has been decisive to improve them. It provides results on samples of the respiratory tract and blood in few hours and this information allows to transform an empirical treatment into a targeted one earlier. Polymerase Chain Reaction (PCR) is an example of these molecular techniques and has greatly developed in last years. Main advantages given by these procedures are [12]: i) High negative predictive value for studied microorganisms, ii) High positive predictive value for genotypic markers of resistance and iii) Increased detection yield compared to standard culture. However, they also have several limitations: i) Clinical significance of qualitative detection debatable (sample dependent), ii) Interpretation of (semi)quantitative result, iii) Interpretation of *mixed* detections and iv) Colonization microorganisms of doubtful clinical significance.

Despite these rapid techniques have dramatically improved time response of microbiological laboratory, it is early to make general recommendations about their use. In any case, progress in reducing time for identification of microorganism and resistance mechanisms is evident. Potential impact is especially relevant for sicker patients, such as ones with VAP or immunosuppressed. However, conventional bacteriological culture is still essential for the correct interpretation of results

Table 1 **Strengths, Weakness, Opportunities and Treats (SWOT) and Correct, Adapt, Maintain y Explore (CAME) analysis.**

SWOT analysis	
Strengths	Weakness
Motivation, capacitation, values, and compromise (attitude and aptitude).	Toxic competitivity between different medical specialities.
Effort culture.	Apathy.
Opportunities	Treats
Strategic alliances between study groups (SG).	SG with same fields of interest and competition between them.
Strategic alliances between SG and Pharmaceutical Industry.	
Execution of inversions and grants.	
CAME analysis	
Correct the Weakness	Adapt to the Threats
Empowerment SG.	Stimulation of own identity and mark.
Stimulation of members of SG.	Create differential value.
Renovation of board of directors.	To search for alliances.
To improve attraction of new members.	
Generational replacement.	
Diffusion in social networks.	
Maintain the Strengths	Explore the Opportunities
Awards for young investigation and publications.	Consensus documents and recommendations.
Awards for clinical cases.	Own clinical trials and epidemiological studies. Derived publications.
Relationship among Sepsis Code and with foundations.	To improve web page.

and decision making. Moreover, the development and improvement of conventional microbiology techniques continue to play an important role in obtaining better results [16].

Actualization in pneumonia. New documents driven by Spanish medical societies. Eleven medical societies collaborated in 2022 to prepare two documents to actualize knowledge about CAP, HAP, and VAP [17, 18]. These societies were GEIPC-SEIMC (critical patient infection study group, Spanish Society of Clinical Microbiology and Infectious Diseases), SEQ (Spanish Society of Chemotherapy), Infurgsemes-SEMES (Emergency Department Infection Study Group, Spanish Society of Emergency Medicine), GEVAC-SEIMC (Vaccines Study Group, Spanish Society of Clinical Microbiology and Infectious Diseases), GTEIS-SEMICYUC (Working Group on Infectious Diseases and Sepsis-Spanish Society of Intensive Care Medicine, Critical Care and Coronary Units), GEMARA-SEIMC (Task Force on Mechanisms of Action and Antimicrobial Resistance, Spanish Society of Clinical Microbiology and Infectious Diseases), GEIRAS-SEIMC (Healthcare-associated Infection Study Group, Spanish Society of Clinical Microbiology and Infectious Diseases), SEPAR (Spanish Society of Pneumology and Thoracic Surgery), SEGG (Spanish Society of Geriatrics and Gerontology), SEDAR-GTIPO (Perioperative Infections Task Force, Spanish Society of Anaesthesiology, Resuscitation and Pain Therapy), and SEHAD (Spanish Society of Hospital at Home). This collaborative effort was preceded by a SWOG and CAME analysis to perform a good strategy, as can be seen in Table 1.

Experts wrote about ten important issues about community-acquired and nosocomial pneumonia.

Most relevant issues for CAP

Changing aetiology. Thanks to introduction of syndromic panels [19], proportion of pneumonia caused by identified bacteria grew from 15-30% to 62-71%, compared to classic methods, such as cultures [20, 21]. Also, the impact of COVID-19 made *Haemophilus influenzae* and *Staphylococcus aureus* were more frequent than *Streptococcus pneumoniae* [22].

Diagnostic procedures [23–25]. *Primary care, outpatient clinic and long-term facilities*: Only rapid antigen detection of SARS-CoV-2 in nasopharyngeal swab is recommended for vulnerable patients, such as aged ones. *Emergency department*. Recommended: rapid antigen detection of SARS-CoV-2 in nasopharyngeal swab. In severe cases: gram stain and culture of respiratory secretions, blood culture, urinary antigen test for *S. pneumoniae* and *Legionella pneumophila* and molecular tests for detection of bacterial and viral pathogens. In patients empirically treated for methicillin-resistant *S. aureus* (MRSA): nares screening for MRSA. Procalcitonin is not recommended to determine initiation of antibacterial therapy.

Use of corticosteroid therapy. Risks (corticosteroid in-

Table 2 Initial treatment strategies for patients with CAP. Adapted from Candel *et al.* [17].

Primary care regimen	Hospital admission regimen	ICU admission regimen
Oral amoxicillin 1g/8h or oral amoxicillin-clavulanic 875/125 mg/8h (if asthma or COPD) or cefditoren 400mg/12h (alternative)	Ceftriaxone 2g/24h iv or cefotaxime 2g/8h iv or ceftaroline 600mg/12h iv (if post-influenza pneumonia or risk of *S. aureus*)	Ceftriaxone 2g/24h iv or cefotaxime 2g/8h iv or ceftaroline 600mg/12h iv
Plus	Plus	Plus
Macrolide (oral azithromycin 500mg/24h/ 3 days or clarithromycin 500mg/12h)	Oral/iv macrolide (azithromycin 500mg/24h /3 days or clarithromycin 500mg/12h)	Macrolide (azithromycin 500mg/24h iv or clarithromycin 500mg/12h iv) or quinolone (levofloxacin 500mg/12h or moxifloxacin 400mg/24h)
or	or	
Levofloxacin500mg/12h (1-2 days) and then 500mg/24h or Moxifloxacin 400mg/24h	Levofloxacin 500mg/12h iv (1-2 days) and then 500mg/24h or moxifloxacin 400mg/24h iv	If risk factors for MDR bacteria: Meropenem 1g/8h iv + Levofloxacin 500 mg/12h iv + Ceftaroline 600mg/12h iv or Linezolid 600mg/12 h iv

Table 3 Pneumococcal vaccination guidelines in Spain. Adapted from Candel *et al.* [17]

Population group	Recommended pattern	Modifications in autonomous regions
Over 65 years without risk factors	PPSV23v (1 dose)	PCV20v or PCV13v (1 dose)
Over 18 years with chronic pathology: chronic cardiovascular and respiratory disease, severe neurological and neuromuscular disease, chronic liver disease, diabetes mellitus, celiac disease, institutionalized persons.	PPSV23v 1 dose + Revaccination each 5 years	PCV20v or PCV13v (1 dose)
Over 18 years high risk groups: immunodeficiencies and complement system deficiencies, immunosuppressive treatment, asplenia or severe splenic dysfunction, HIV infection, chronic renal failure and nephrotic syndrome, transplant, CSF fistula, cochlear implant, history of invasive pneumococcal disease, liver cirrhosis and chronic alcoholism, Down syndrome.	PCV13v (1 dose) + PPSV23v (1 dose) (at least 8 weeks)	PCV20v (1 dose) + PPSV23v (1 dose) (at least 8 weeks)

PPSV23v: 23-valent Pneumococcal polysaccharide vaccine. PCV13v: 13-valent pneumococcal conjugate vaccine, PCV20v: 20-valent pneumococcal conjugate vaccine. HIV: Human Immunodeficiency Virus. CSF fistula: cerebrospinal fluid fistula.

duced hyperglycaemia) and potential benefits (to avoid ICU admission and reduction of treatment failure) must be balanced towards a personalized medicine [26, 27]. A deeper review will follow in next sections, but the most important remarks are: Influenza pneumonia. Clinicians must avoid corticosteroid [28], refractory septic shock (in context of respiratory focus origin). Corticosteroid therapy has demonstrated benefit [29]. Other situations such as COVID-19, autoimmune disease, or concurrent asthma of chronic obstructive pulmonary disease (COPD), employment of corticosteroid can be considered [30, 31].

Recommended initial treatment is shown in Table 2 [32]. The duration of treatment should be individualized according to clinical stability with a minimum of 5 days. Risk factors for multidrug resistant (MDR) bacteria include prior respiratory isolation of MRSA or *Pseudomonas aeruginosa*, severe COPD, bronchiectasis, or recent hospitalization and receipt of parenteral antibiotics (in the last 3 months).

Main risk factors for readmission. CAP related [33–35]: worsening signs and symptoms of CAP, treatment failure, clinical instability at discharge, PSI (pneumonia severity index) ≥ 4, leucocytosis over 12000/mm^3, and multidrug-resistant bacteria. *Non-CAP related* [36–38]: comorbidities, age over 65 years, Charlson comorbidity score over 2, coronary heart disease, COPD, non-metastatic cancer, complicated diabetes, chronic kidney disease, ≥3 previous admissions, chronic respiratory failure, heart failure, chronic liver disease, and discharge to hospital at home unit. Dementia was a protective factor for readmission, despite aspiration risk.

Other issues were the Spanish recommendations for *pneumococcal vaccination* (Table 3) and new advances given by *artificial intelligence* are available, such as machine learning for the prediction of sepsis [39] and interpretation of chest radiographs [40].

Most remarked issues in HAP and VAP (some of them are showed in other parts of the present document).

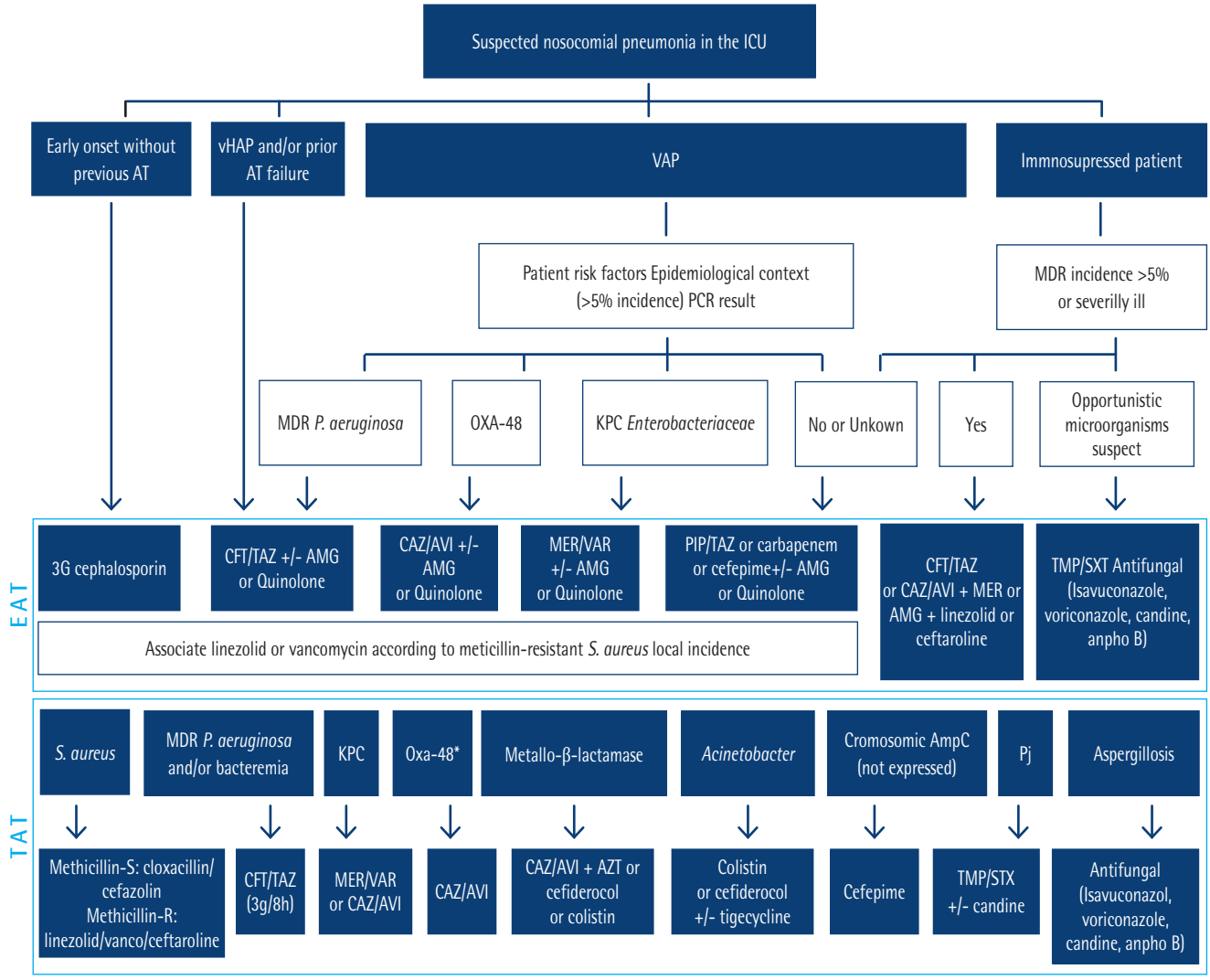

Figure 1 | **Modified PANNUCI algorithm from empirical to targeted treatment on nosocomial pneumonia in ICUs in European countries (both immunocompetent and immunosuppressed). Adapted from *Candel* et al. [18]**

AT: antimicrobial therapy; vHAP: ventilated hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; MDR: multidrug resistant; PCR: polymerase chain reaction; CFT/TAZ: ceftolozane/tazobactam; CAZ/AVI: ceftazidime/avibactam; PIP/TAZ: piperacillin/tazobactam; AMG: aminoglycoside; AZT: Aztreonam; EAT: empirical antimicrobial treatment; TAT: targeted treatment; OXA-48: OXA-48 Carbapenemase; KPC: *Klebsiella pneumoniae* Carbapenemase; MER-VAR: meropenem-vaborbactam; IMI-REL: imipenem-relebactam; ESBL-E: extended spectrum beta-lactamase-producing enterobacteria; PJ: *Pneumocystis jirovecii*. * If Oxa-48 susceptible to CAZ/AVI.

Molecular techniques. They are very useful for rapid diagnosis of HAP and VAP. They detect a wide range of microorganisms, with a variety of commercial panels. The range of answer time goes from 20 to 120 minutes. They have demonstrated an improvement in health, mortality, and a good cost/benefit profile. They are especially helpful for immunocompromised patients and for detection of viruses such as SARS-CoV-2 [41–45].

Nowadays, two main guidelines recommend different samples to reach microbiological diagnosis in VAP. The American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guideline [46] recommends tracheal aspiration, which is the easiest, safest, and cheapest way, although it is vulnerable to upper respiratory tract contamination, so sometimes it is difficult to differentiate colonization from real infection and a derived risk of overuse of antibiotics exists. On the other hand, the International ERS/ESICM/ESCMID/ALAT (European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, Latin American Thoracic Association) guideline [47] suggest the use of bronchoscopy with bronchoalveolar lavage (BAL), that requires trained staff, but it obtains a lower respiratory tract sample, has higher specificity, easily

Table 4 Causes of therapeutic failure in patients with HAP-VAP. Adapted from Candel *et al.* [18]

Cause	Recommendation
Inadequate antibiotic treatment	Escalate based on microbiological results.
Sub-therapeutic antibiotic concentrations	Increase antimicrobial dosing. Use extended or continuous antibiotic infusions to optimize PK/PD parameters
New pathogens isolated	Antimicrobial treatment according to microbiological data
Undrained pyogenic focus (i.e., empyema)	Therapeutic drainage
Drug fever	Change antibiotic treatment
A non-infectious illness presenting as HAP	Management as appropriate

PK/PD: pharmacokinetics/pharmacodynamics.

distinguishes infection from colonization and is safe. Finally, mini-BAL is a reasonable alternative when bronchoscopy is not available [48–51].

Immunosuppressed patients can benefit from a wide range of microbiological procedures [18]. Some of them are: i) Microbiological stains or respiratory secretions, with immediate results and low costs. Despite these advantages, there are derived risk of false negative results, and they are also observer dependent, ii) Traditional culture of respiratory specimens and blood, which are time dependent and have medium-low performance, iii) Detection of fungal antigens, such as galactomannan in respiratory samples or blood; and (1-3)-β-D-glucan or cryptococcal antigen in serum sample. More useful in neutropenic patients and some techniques are not completely validated, iv) PCR (polymerase chain reaction) in respiratory samples, nasopharyngeal swab, or blood. It is very sensitive but with risk of false positive (colonizing microorganisms) and false negative (inadequate sample, microorganisms not included in the panel), v) Direct fluorescent antibodies directed against certain microorganisms, vi) Detection of soluble antigens in urine.

The prior *PANNUCI algorithm* for antibiotic treatment of pneumonia [52] has been updated [18]. It is shown in Figure 1. Use of antibiotics for *hospital at home* (HaH) is an useful tool to improve quality of life of some patients with HAP that requires intravenous treatment for a long time and reach clinical stability. New devices such as electronic and elastomeric pumps allow a safe administration at home [53–55]. Finally, a review of causes of *therapeutic failure and recommendations* to solve them can be seen in Table 4 [18].

Allergy to beta-lactam antibiotics. Allergy to beta-lactam antibiotics is a frequent problem among patients and in Spain it is estimated that a 10-12% of the population has some type of hypersensitivity and women are more often affected. Overall, 17% of all these adverse drug reactions are severe and 0.6% are the cause of death [56, 57]. Clinical spectrum of allergic reactions is very wide. They include cutaneous reactions, anaphylaxis, blood dyscrasias and kidney diseases. Amoxicillin-clavulanic is the antibiotic more often involved, although more of the reactions are mild. Cases caused by piperacillin-tazobactam and meropenem are less frequent, but their occurrence has been increased in last years and their severity is higher [58]. Moreover, people who are allergic to beta-lactam antibiotics have worse outcomes: they are more days in hospital, have higher rates of hospital readmission, costs, ICU stay and mortality; have more postsurgical complications and higher risk of *Clostridioides difficile* diarrhoea and multidrug resistant bacterial infections [56, 59, 60]. In addition, alternative antibiotics such as quinolones have an unfavourable adverse reaction profile, with publication of safety notes by regulatory agencies [61].

Despite being a frequent problem among general population, different studies have demonstrated that only 18.3% to 28.6% of people who claim being allergic to beta-lactam are really allergic to them [62–64]. This false label limits possibilities of treatment and potentially causes worse outcomes as has been mentioned.

Chemical structure of beta-lactam antibiotics is important because it determines cross reactivity between different molecules. They have a shared beta-lactam ring, a specific ring for each group and one or more lateral chains, that can be similar between different beta-lactam antibiotics, even if they are of different families. Generic chemical structure is showed in Figure 2 [65–67].

Owing to their different chemical structure, hypersensitivity to penicillin, for example, does not mean hypersensitivity to other beta-lactam antibiotics. In fact, cross reactivity between first generation cephalosporins and penicillin is less than 10%. Lateral chain is a good predictor of cross reactivity, so that different beta-lactam antibiotics with a similar lateral chain have a relative risk of cross reactivity of 3 (confidence interval -CI- 1.6-5.5), whereas second and third generation cephalosporins, such as ceftriaxone, have a very low chance of cross reactivity with penicillin, due to their different lateral chains [65, 66, 68, 69]. In fact, 75 - 97% of penicillin allergic patients tolerate cephalosporins, and 99% tolerate aztreonam and carbapenems. Although aztreonam has been classically considered secure in these patients, it shares the same lateral chain than ceftazidime and cefiderocol, so cross reactions are expected between them and its use in patients allergic to these

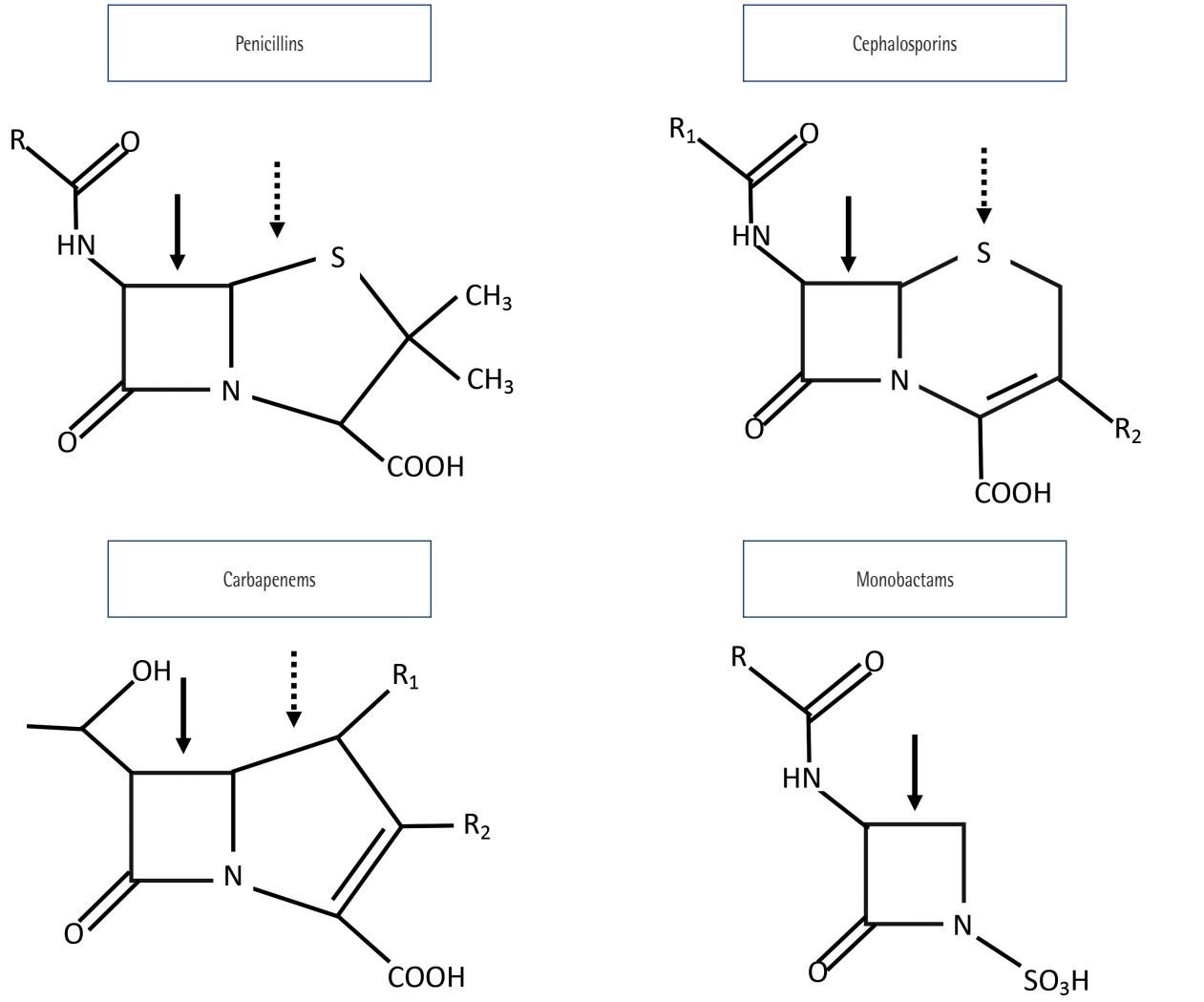

Figure 2 | **Beta-lactam structure**

Solid arrow: beta-lactam ring. Dashed arrow: group ring. R, R1, R2: lateral chains.

specific cephalosporines is not recommended. In the case of carbapenems, a history of penicillin allergy contraindicates their use, but in practice it is important to know result of historical cutaneal allergy test against penicillin, which has a high negative predictive value [64]: in case it is negative, use of carbapenems is considered secure; in case it is positive or unknown, carbapenem should be administrated in a gradual way, with increasing concentration and with narrow surveillance of allergic reactions [70–73] .

So, beta-lactam allergy is a heterogeneous problem because a patient can be allergic to a specific family (e.g. aminopenicillins) but can tolerate other families (e.g. carbapenems). Moreover, false label of beta-lactam allergy is a frequent issue that can be dangerous because it can lead to worse outcomes as has been mentioned. So, it is very important to take a detailed clinic history and consultation with allergology if available [74]. PEN-FAST is an instrument designed to stratify risk in these patients and it evaluates time since allergic reaction, clinic manifestations and severity of them, and treatment required for reaction [75]. So, after a careful evaluation, a patient can be classified as not allergic if he has an adverse reaction such as vomiting or diarrhoea; mild reaction probably not mediated by IgE, so cephalosporins of third generation and newer, carbapenems and aztreonam can be used; and severe reactions, that can be mediated by IgE, such as anaphylaxis, or not mediated by IgE, such as interstitial nephritis. In these last cases, only aztreonam can be employed. In all cases, a subsequent evaluation by allergy service is strongly recommended. Other instruments have been developed to evaluate the risk

Table 5 Empirical treatment in patients allergic to beta-lactam antibiotics. Adapted from Barberán *et al.* [79]

	Low risk of allergic reaction	High risk of allergic reaction
CAP	Levofloxacin 750 mg/24 h vo If severe: Ceftriaxone 2 g/24 h iv plus Azithromycin 500 mg/24 h vo or Levofloxacin 750 mg/24 h iv	Levofloxacin 750 mg/24 h iv
Early HAP-VAP (less than 5 days in hospital)	Ceftriaxone 2 g/24 h iv or Levofloxacin 750 mg/24 h iv	
Late or severe HAP-VAP	Ceftazidime 2 g/8 h iv or Meropenem 1-2 g/8 h iv. Consider add: Linezolid 600 mg/12 h iv or Vancomycin 30 mg/kg/d in 2-3 doses iv	Aztreonam 2 g/8 h plus Linezolid 600 mg/12 h iv or Vancomycin 30 mg/kg/d in 2-3 doses iv
Lung abscess or aspiration pneumonia	Ceftriaxone 2 g/24 h iv plus Clindamycin 600 mg/8 h iv	Aztreonam 2 g/8 h plus Clindamycin 600 mg/8 h iv

of cross reaction and they have demonstrated an increment in utilization of beta-lactam without a higher rate of adverse effects [76, 77].

Recommended empirical antibiotic treatment is shown in Table 5. Recommended duration of treatment is 3-5 days in CAP, 8 days in HAP-VAP, and individualized until drainage in the case of lung abscess. Clinicians also must consider antibiotic coverage of *S. aureus* and/or *P. aeruginosa* if needed. If a beta-lactam antibiotic is used, they may perform a previous controlled exposition trial [56]. As it has been stated, it is important to eliminate false allergy labels and to stratify risk. Allergy consultation, if available, is strongly recommended. Alternatives with non-beta-lactam antibiotics, such as moxifloxacin, omadacycline, eravacycline or plazomicin may be considered for some patients with multidrug resistant bacteria [78–80]. Currently, the optimized management of beta-lactam allergy is included in stewardship strategies or programs.

Zero Pneumonia. The Zero Pneumonia (ZN) project is a multifactorial intervention proposal based on the simultaneous application of a package of measures to prevent VAP. Its intention is to reduce the infectious complications in Spain. The project is sponsored by the Quality Agency of the Ministry of Health, Social Policy, and Equality (MSPSI) with the collaboration of the Spanish Society of Intensive Care Nursing and Coronary Units (SEEIUC) and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC). Zero Bacteriemia project was developed previously, and its structure was used to implement ZN project. It is an ambitious project that involves the MSPSI Quality Agency, the Health Departments of the Autonomous Communities (AACC) and the management team of several national hospitals. It also includes the collaboration of doctors and nurses from most ICUs in the country and different working groups of the SEMICYUC. The main objective of the ZN project is to reduce the national VAP rate to less than 9 episodes per 1,000 days of mechanical ventilation, which means a 40% reduction respect to previous rates (2000-2008) and a 25% reduction compared to 2009 and 2010 rates.

To achieve it, medical doctor and nurses, appointed by their respective societies, defined ten recommendations. Seven of them have the highest scientific evidence and are obligatory [81]. They are: Training of staff in airway manipulation, control of pneumotamponade, oral hygiene with chlorhexidine (0.12-0.2% every 6-8h), hand hygiene, avoid supine position whenever possible, promoting the process of respiratory mechanical weaning, avoid the scheduled change of humidifiers and tracheal tubes. Another three recommendations are highly recommended, but at the beginning they were not mandatory: Selective decontamination of the digestive tract, aspiration of subglottic secretions, use of systemic antibiotics during intubation in patients with a low level of consciousness.

The applications of these measures made incidence of VAP decrease until 5.41 episodes per 1,000 days of mechanical ventilation in 2019. However, COVID-19 pandemic made it rise to 19.99 in 2021. Therefore, the latest ZN guideline made all recommendations mandatory. This change, along with control of COVID-19 pandemic, made incidence of VAP decreases to 8.55 [81].

Finally, aetiology of VAP has maintained without great changes in the last 10 years, with *P. aeruginosa* and *K. pneumoniae* predominating among Gram-negative Bacilli (GNB), and methicillin-susceptible *S. aureus* among Gram Positive Cocci (GPC). As resistance mechanisms associated with GNB,

Table 6 ATS/IDSA criteria to define severe CAP. Adapted from File *et al.* [84]

Major criteria	Minor Criteria
Septic shock treated with vasopressors Respiratory failure necessitating mechanical ventilation	Respiratory rate ≥ 30 bpm Confusion or disorientation Hypothermia (temperature < 36ºC) Hypotension necessitating aggressive fluid resuscitation Leukopenia (<4000 cells/mm^3). Thrombocytopenia (<100000 platelets/mm^3). Uremia: BUN ≥ 20 mg/dL. Ratio PaO_2 to FiO2 ≤ 250 Multilobar (≥2) infiltrates

bpm: breath per minute, BUN: blood urea nitrogen level, PaO_2: partial pressure of arterial oxygen, FiO_2: fraction of inspired oxygen.

extended-spectrum beta-lactamase (ESBL) producing Enterobacterales, multi-resistant *Pseudomonas* spp, and metallo-beta-lactamase producing GNB stand out. Meropenem and linezolid are the most used antibiotics, whereas utilization of piperacillin/tazobactam has decreased and the appearance of new molecules have allowed the development of new therapeutic regimens [14, 29, 81].

Therapeutic optimisation in community-acquired pneumonia

Community-acquired pneumonia in intensive care unit (ICU). Pneumonia is an important cause of death worldwide. It was the first cause of death at the end of twentieth century and nowadays is the second cause, only overcome by cardiovascular diseases [82]. Moreover, it frequently causes the death of aged people [83]. Among CAP that require ICU admission, mortality have maintained high (around 30%), despite efforts to reduce it [84–87]. Apart from distress syndrome, which severity is correlated with likelihood of death, other factors related with higher risk of decease are advance age, previous antibiotic therapy, comorbidities, multiorgan failure and an inadequate empiric antibiotic treatment [88]. Another factor related with higher mortality is delayed intubation in patients who needed it [89].

The main identified aetiology of CAP is *S. pneumoniae*, identified in more than 80% of isolates, but its prevalence has become slightly lower in last years. It is followed by other microorganism such as *Streptococcus* spp., *Haemophilus* spp., enterobacteria, *Pseudomonas* spp. and others [21,90,91]. However, in 50% of pneumonias, etiologic agent is not identified. This lack of identification is related with antibiotic treatment before obtaining sample and non-invasive tests [92]. Decreased susceptibility to penicillin of *S. pneumoniae* is observed in some pneumococcal pneumonia. An intermediate susceptibility can be observed in 5-10% of cases, while high resistance is confirmed in less than 4% of all cases [93]. *S. pneumoniae* has a decreased susceptibility to ceftriaxone in 5-10% of isolates, depending on studied region. In contrast, quinolones and ceftaroline maintains an excellent profile, with susceptibilities of almost all studied isolates [94].

Severe CAP pneumonia is defined as a CAP with a major criterion or at least 3 minor criteria established by the American Thoracic Society and Infectious Diseases Society of America -ATS/IDSA- [84,95]. These criteria are shown in table 6.

Recommended empiric antibiotic treatment can be read in table 2. Guidelines worldwide recommend a combination of a beta-lactam plus macrolide or quinolone [29,96–98]. Due to potential serious adverse effects of quinolones [61] and proven benefits of macrolide combinations of 3 days, this last is the preferred option. Election of beta-lactam is an important issue with new evidence emerging in last years. Traditionally, choice of election has been ceftriaxone or cefotaxime. An ideal antibiotic in severe CAP has these qualities: to reach an adequate serum concentration, to compensate distribution volume of critic patient, to create a high gradient to tissue, to reduce quickly bacterial charge and to achieve enough concentration to avoid mutant selection [99]. Two relatively news beta-lactam antibiotics have properties like the ones described. Ceftobiprole demonstrated a better rate of improvement than comparator [100]. Ceftaroline also proved better outcomes than ceftriaxone in different settings and in presence of bacteriemia [101–103]. Duration of treatment must be tailored to patient evolution, but in many cases five days is enough. Procalcitonin serum levels (PCT) can guide this, but there is not a specific threshold to take a decision. Dynamic changes, considering clinical state of patient, may be helpful [96,104]. If viral aetiology is demonstrated, in absence of signs of bacterial coinfection, antibiotic therapy can be safely stopped. Signs of bacterial coinfection are positive culture, radiographic findings suggestive of bacterial origin, high white-cell count (>15000/mm^3), high c reactive protein (>150 mg/L) and/or PCT over 0.25 ng/mL.

So, to make mortality rates become lower in severe CAP,

Table 7 **Available options for sequential treatment of pneumonia. Adapted from Barberán *et al.* [116]**

	Advantages	Disadvantages
Cefditoren	Almost no pneumococcal resistance Administration each 12 hours Dose of 400 mg each 12 hours has an optimal pharmacokinetic profile, even against *S. pneumoniae* with decreased penicillin susceptibility Lowest risk of resistance selection	Bioavailability of 20%. It can improve with food [109]
Amoxicillin-clavulanate	Low resistance rate Bioavailability of 60%	Commercial formulation (875/125 mg) needs to be given each 8 ours High dose of amoxicillin (2000 mg twice a day) is needed for *S. pneumoniae* with decreased penicillin susceptibility and to avoid resistance selection Highest ecological impact
Levofloxacin	Administration each 12 -24 hours Highest bioavailability (>95%)	Risk of severe side effects: QT syndrome, tendonitis, retinal detachment, aortic dissection, dysglicemia, psychiatric side effects High dose (500 mg twice a day) is needed to avoid resistance selection

an energic approach is needed. Focus on vulnerable patients, early intubation in people who need it and wisely use of antibiotic therapy might aid to achieve this objective.

Sequential treatment in community-acquired pneumonia. Antibiotic stewardship can be defined as a set of strategies to promote the responsible use of antimicrobials for the purpose of protecting public health [105]. A lot of interventions can contribute to this objective, but some of them are easier to implement than others and with stronger evidence of cost-saving results, such as formulary restrictions, batching of intravenous antimicrobials, therapeutic substitutions, and intravenous-to-oral conversions -sequential therapy- [106]. This last one intervention is also a basic element of stewardship programs in pneumonia treatment [107]. There are three kinds of intravenous-to-oral conversions [108]:

- Sequential therapy. To replace the same antibiotic with an oral formulation. E. g. substitution of levofloxacin iv (intravenous) for levofloxacin, moxifloxacin (or perhaps or in the near future, delafloxacin po (per oral)).
- Switch therapy. To substitute an antibiotic for an equivalent with an oral formulation. The best candidate for sequential therapy since ceftriaxone, by in vitro activity and with the best pharmacodynamic profile, is cefditoren at a dose of 400 mg every 12 hours. Its absorption improves if taken with food [109].
- Step down therapy. To replace an antibiotic for another of other class with an oral formulation. E. g. substitution of ceftriaxone iv for levofloxacin po.

Sequential therapy is a universal recommendation in current guidelines for the treatment of pneumonia [95,96]. To do so, patient must have reached clinical stability, defined with the following criteria [29,110]: Resolution of vital sign abnormalities (heart rate less than 100 beats per minute, respiratory rate less than 24 breaths per minute, systolic blood pressure more than 90 mmHg, arterial oxygen saturation more or equal to 90% with usual oxygen flow for the patient, temperature less than 37.8ºC, normal mental status) and the ability to eat.

In a study conducted in Japan, sequential therapy was performed in 30.1% of patients, and was more frequent among mild patients and in people treated by pulmonologists [111]. Early intravenous-to-oral conversion of antibiotic therapy is safe, with the same rate of mortality, recurrent infections, and treatment success than exclusive intravenous therapy; and it is associated with a shorter length of hospital stay and lower costs [112,113].

Despite its advantages, there are resistances to implant sequential therapy. Some identified barriers are wrong concepts, practical issues, factors related to organization and insufficient medical education [114]. To overcome these barriers, it is necessary to establish a clear hospital program, with the identification of patients who can benefit from early switching from intravenous treatment to make recommendations to physicians and to maintain an open channel of two-way communication to create an appropriate culture. Finally, it is important a surveillance of these patients to implement improvement measures [108].

Characteristics of an ideal oral antibiotic to implement a sequential therapy are [115] similar antimicrobial spectrum, high bioavailability, favourable pharmacokinetic characteristics (oral route, administration every 12 to 24 hours), low resistance selection and, if possible, low cost. In table 7, available options to swich from an intravenous to an oral antibiotic treatment are shown. Due to high rate of pneumococcal resistance of ce-

Table 8 Surveillance of bacteria of interest. Adapted from Parente *et al.* [135]

Bacteria	Sample	PPV	NPV
MRSA	Nasal exudate	Moderate	Very high
CPE	Perineal exudate	Moderate	Very high, combined with local epidemiology
PAER	Respiratory or perineal	High	Low

CPE: carbapenemase producing enterobacteria, PAER: *P. aeruginosa*, PPV: positive predictive value, NVP: negative predictive value.

Table 9 Mechanisms of resistance and susceptibility of new beta-lactams. Adapted from Doi *et al.* [151]

	Carbapenemase					
	Class A	Class B	Class D			
	KPC, GES	MBL: VIM, NDM, IMP	OXA-48	PAER MR	*Acinetobacter*	*S. maltophilia*
Ceftazidime-avibactam	S	R	S	S	R	R
Ceftolozane-tazobactam	R	R	R	S	R	R
Imipenem-relebactam	S	R	R	S	R	R
Meropenem-vaborbactam	S	R	R	R	R	R
Cefiderocol	S	S	S	S	S	S

R: resistant, S: susceptible, PAER MR: *P. aeruginosa* multi-drug resistant.

fixime, almost 70% of isolates, this antibiotic is considered inappropriate. Finally, cefuroxime in usual dosage (500 mg twice a day) does not reach enough serum concentration to be active against *S. pneumoniae* [61,116–119].

Therapeutic optimisation in healthcare-associated pneumonia

Antibiotic therapy in hospital-acquired pneumonia and ventilation associated pneumonia. Empiric antibiotic treatment for HAP and VAP in ICU is tailored to microbiologic results of samples, which usually last 24 to 48 hours to be known with traditional microbiological methods [120]. In Spain there is intensive surveillance of aetiology of infections in ICUs [121]. This surveillance shows that the most frequent microorganisms are *P. aeruginosa* (17.56%), *S. aureus* (10.43%) and *K. pneumoniae* (10.32%). Among the ten most common microorganisms isolated are also *S. maltophilia* (5.49%), *A. fumigatus* (2.63%) and cytomegalovirus -CMV- (2.09%), which are not routinely covered by empirical treatments. Moreover, around 20% of all empiric treatments for bloodstream infections do not treat the aetiology properly and the main predictor of empiric treatment failure is the isolation of a resistant microorganism [122]. Delayed appropriate treatment is associated with higher length of antibiotic treatment, hospital stay, disability and costs [123]. An early BAL is recommended for these infections to obtain a good sample for microbiological analysis and to adjust empiric treatment as soon as possible [120].

Current guidelines recommend empiric treatment with an antibiotic against methicillin-resistant *S. aureus* -MRSA- (linezolid or vancomycin) with a combination of two antibiotics with action against *P. aeruginosa* (beta-lactam plus fluoroquinolone or aminoglycoside or polymyxin) [6,7]. European guideline adapts empiric antibiotic coverage attending to severity and local epidemiology [124]. As antibiotic consumption in Spain shows, these recommendations are often followed [121]. A common suggested combination is meropenem plus linezolid plus amikacin, but due to predominant profiles of resistance of microorganisms, there is a high risk of a functional monotherapy of aminoglycoside, which is a not recommended option [7,121] . The most important risk factors for infection by a multidrug resistant microorganism are [125–134]: antibiotic pressure, immunosuppression, comorbidity, hospitalization-length of stay, severity of illness, local epidemiology, colonization of the patient by resistant microorganism and diagnostic and therapeutic invasive procedures performed.

There are some strategies that can help to design a more precise empiric treatment. These approaches are a potent tool to anticipate classical microbiological results, such as surveillance of colonization by bacteria of interest [135–138]. In table 8 the most used techniques are show, knowledge about local and regional epidemiology, and trends in resistance profile. Among enterobacteria in Spain, the most frequent kind of carbapenemase is OXA-48, but other types such as KPC are also rising [139]. In contrast, frequency of carbapenemase production by PAER is lower [140], previous antibiotic pressure in-

creases risk of antibiotic resistance, especially in case of PAER [141], microscopic examination of samples and detection of resistance genes by molecular techniques such as PCR [120,142].

There are recently commercialized beta-lactam antibiotics that have a higher rate of susceptibility than older ones against PAER. Also, aminoglycosides and colistin maintain low rates of resistance [143], but new beta-lactams have demonstrated better results than combinations of older ones [144–150]. In table 9 there is a review of mechanisms of resistance and susceptibility of different recently developed beta-lactams [151,152].

Attending to all aspects commented in last paragraphs, a new approach to empiric treatment has been developed by Spanish Medical Societies, that is available in Figure 1 [18]. As it is shown, a suggested empirical treatment guided by clues given by patient profile, local epidemiology, gram staining and molecular techniques is strongly recommended. Empiric treatment against PAER must include a beta-lactam antibiotic, although double antibiotic empiric regimen is optional and it may be prescribed in case or risk of therapeutic failure, to achieve synergic action and to optimize pharmacokinetic and pharmacodynamic properties [153].

Although European Guidelines recommends a duration of treatment of less than 7 days [6], length of treatment is not well determined in case of multidrug resistant microorganisms [18]. Regarding the duration of antibiotic treatment for *P. aeruginosa* pneumonia, a recent clinical trial failed to demonstrate non-inferiority of 8 days versus 15 days. Moreover, the shorter length of treatment was associated with increased recurrencies [154].

Finally, benefit of nebulized antibiotics for VAP has been argued in last years. Pneumonia is an infection of high inoculum and due to bronchi obstruction and atelectasis, nebulized antibiotics fails to achieve enough concentration in target tissues of animal models [155–158]. In humans, different devices have been used to give these treatments, and membrane inhalers are preferred in ventilated patients [159]. Experts advise to avoid nebulized antibiotics for treatment of HAP and VAP, due to the lack of effectiveness in reducing mortality and length of ICU stay, and a high rate of respiratory adverse effects [160,161]. Whereas inhaled antibiotics for treatment are not recommended, amikacin may prevent VAP if given to patients recently intubated [162].

HAP-VAP by producing-carbapenemase enterobacteria non metallo-beta-lactamase (non-MBL CRE). Infectious Diseases Society of America (IDSA) in 2023 has proposed several recommendations for the treatment of infections caused by resistant bacteria [163]. Ceftazidime-avibactam and meropenem-vaborbactam are two current alternatives in the treatment of HAP-VAP caused by non-MBL CRE, especially carbapenemases OXA-48 like and KPC types.

Ceftazidime-avibactam has excellent activity against bacteria that produce β-lactamases of Ambler class A and C, as well as some of group D (OXA), including extended-spectrum β-lactamases (ESBL), AmpC, KPC-type carbapenemases and OXA-48 [164]. Data on the effectiveness of ceftazidime-avibactam in critically ill patients, such as mechanically ventilated patients, are limited. In 2020, a retrospective observational cohort study in central Greece compared critically ill and mechanically ventilated patients (41 subjects) suffering from CRE infections receiving ceftazidime-avibactam to 36 patients who received other appropriate available antibiotic therapy, such as polymyxin B, tigecycline and aminoglycosides. There was a statistically significant improvement in the Sequential Organ Failure Assessment (SOFA) score on days 4 and 10 in the ceftazidime-avibactam group compared to that in the control group. Ceftazidime-avibactam was better than other treatments in all evaluated outcomes: microbiological eradication, clinical cure, and mortality. Illness severity was also associated with mortality. In conclusion, a ceftazidime-avibactam-containing regime was more effective than other available antibiotic agents for the treatment of CRE infections in the high-risk, mechanically ventilated ICU population evaluated [165].

Despite these encouraging results, resistance to ceftazidime-avibactam has developed in recent years, such as KPC-2 and KPC-3 variants. Resistance caused by the plasmid with a mutation in the blaKPC-3 gene (D179Y variant, described in the ST258 clone) is a challenge for microbiology laboratory. It reduces the MIC to carbapenems and other beta-lactams, which can lead to false negative result in carbapenemase immunochromatography detection kits. This mutation produces changes in the KPC Ω-loop zone (165–179 positions), it increases the affinity for ceftazidime and meropenem and it restricts binding to avibactam [166].

Meropenem-vaborbactam is another novel antibiotic. Vaborbactam is a serine-β-Lactamase inhibitor, derived from boronic acid. It is defined as Ambler class A inhibitor (especially KPC) and C, but it does not inhibit B and D classes [167]. A Phase 3, multinational, open-label, randomized controlled trial (TANGO II) was conducted from 2014 to 2017 to evaluate the efficacy and safety of meropenem-vaborbactam monotherapy versus best available therapy (BAT) for CRE. Eligible patients were randomized 2:1 to meropenem-vaborbactam (2g/2g over 3 h-8h for 7-14 days) or BAT (mono or combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime-avibactam alone). Efficacy endpoints included clinical cure, day-28 all-cause mortality, microbiologic cure, and overall success (clinical cure + microbiologic eradication). Meropenem-vaborbactam was better than BAT for cure rates and test cure, but there was not a statistically significant difference for day-28-all-cause mortality [145]. As in the case of ceftazidime-avibactam, resistance to this new drug has been described, such as OmpK35 and 36 mutations [168].

Cefiderocol has potent in vitro and in vivo activity against multidrug-resistant (MDR) gram-negative bacilli, including carbapenem-resistant isolates (including A, B, C and D Ambler beta-lactamase classification). Exceptional reduced susceptibility during treatment to cefiderocol have already been reported [169].

Imipenem-relebactam is a new combination of a be-

Table 10 **Differences in the IDSA and ESCMID *A. baumannii* CR infections treatment recommendations. Adapted from Tamma *et al.* [163] and Carrara *et al.* [178]**

IDSA	ESCMID
The use of high doses of ampicillin-sulbactam is recommended (6-9g/day) in combination with another antibiotic at least until clinical improvement is observed. Associate minocycline, tigecycline, polymyxin B or cefiderocol. do not associate fosfomycin, rifampicin or meropenem. It is recommended to use ampicillin-sulbactam, even if it is *in-vitro* resistant.	For patients with *A. baumannii* CR pneumonia sensitive to sulbactam, suggests ampicillin-sulbactam (Low level of evidence)
Consider the use of polymyxin B in combination with another antibiotic, because of limitations of this antibiotic: narrow therapeutic range, suboptimal pulmonary penetration, potential clinical failure, and emergency of resistance during treatment.	For patients with *A. baumannii* CR resistant to sulbactam, polymyxin or high doses of tigecycline are recommended if they are active in vitro. There is not enough evidence and a preferred antibiotic could not be recommended.
High doses of minocycline or tigecycline can be used with at less another antibiotic. Tigecycline is associated with higher mortality rates and should not be used in presence of bacteriemia.	We conditionally advise against the use of cefiderocol for treatment of infections caused by *A. baumannii* CR (low level of evidence).
Cefiderocol should be limited to the treatment of *A. baumannii* CR if other treatments fail, or it is resistant. It is recommended to prescribe it in combined treatment.	Neither combinations are recommended: polymyxin-meropenem (high level of evidence) nor polymyxin-rifampicin (moderate level of evidence).
The use of nebulized treatment is not recommended for respiratory infections.	In high risk and severe-ill patients, a combination of two antibiotics with *in vitro* activity among available therapies should be used: polymyxins, aminoglycosides, tigecycline, sulbactam. (very low level of evidence). If meropenem MIC is less than 8mg/L, combined therapy with meropenem extended infusion is suggested (good practice).

ta-lactam and a beta-lactamase inhibitor. Relebactam has the power to inhibit type A (KPC, GES, IMI) and C (AmpC, PCD) beta-lactamases, but it is useless against type B and D. It also inhibits ESBL. This combination has demonstrated non-inferiority compared to piperacillin-tazobactam in HAP-VAP, with or without bacteraemia [170]. Its safety profile is comparable to that of imipenem-cilastatin. It is a useful alternative in the treatment of HAP-VAP caused by non-MBL CRE type A, in a targeted treatment setting or in settings of high prevalence and clinical suspicion as empirical treatment [171].

Metallo-beta-lactamase-producing *Pseudomonas aeruginosa*. Infections caused by multidrug-resistant Gram-negative bacteria are becoming a worldwide problem due to their increasing incidence and associated high mortality. Carbapenem-resistant bacteria such as *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* are the most important in clinical practice [172,173]. *P. aeruginosa* is presented as one of the main microorganisms causing HAP/VAP in the last few years [18]. Metallo-beta-lactamase (MBL) production has been the cause of therapeutic failures with the antibiotics available in the therapeutic arsenal. However, the appearance of new antimicrobials and the rescue of old known drugs have provided alternatives for this type of isolates [173]. Several teams from the CIBER for Infectious Diseases (CIBERINFEC) led by the Balearic Islands Health Research Institute (IdISBa)/Son Espases Hospital have analysed the evolution of antibiotic resistance in *P. aeruginosa*. The results have recently been published in The Lancet Regional Health-Europe [140]. The work reveals that, in 2022, bacteria showed lower resistance to all the antibiotics evaluated, both the oldest and the newest, which implies that the bacteria were more susceptible to these treatments. Additionally, a significant decrease in the prevalence of multidrug resistance (resistance to three or more families of antibiotics) and extensive resistance (resistance to all, except 1 or 2 families) bacterial profiles was found in 2022 compared to 2017. However, a significant increase in the proportion of strains with the most dangerous mechanism, the production of carbapenemases, has been described. Moreover, it is associated with the dissemination of the hypervirulent epidemic strain ST235. This strain, along with ST175, and others associated with high frequency to MBL production, are great challenges for antibiotic management [140]. Alternatives currently available in MBL-producing *P. aeruginosa* isolates are: cefiderocol, fosfomycin, high doses of amikacin and synergistic combinations [173]. The combination of ceftazidime/avibactam with aztreonam is an attractive alternative in MBL-producing enterobacterales. However, in the case of *P. aeruginosa*, due to the coexistence of collateral mechanisms, such as overexpression of efflux pumps or loss of porins, it is not the preferred alternative if other drugs are available [174].

The novel beta-lactam cefiderocol is stable against different serine- and metallo-beta-lactamases, and, due to its iron channel-dependent uptake mechanism, is not impacted by porin channel loss. Furthermore, the periplasmic level of cefiderocol is not affected by upregulated efflux pumps. The

Table 11 **Differences in the IDSA and ESCMID *S. maltophilia* infections treatment recommendations. Adapted from Tamma *et al.* [163] and Carrara *et al.* [178]**

IDSA	ESCMID
We recommend the use of 2 of the following antibiotics in combination: TMP-SMX, minocycline, tigecycline, cefiderocol or levofloxacin.	Consider combined therapy in severe infections, especially in immunocompromised patients.
We recommend the combination ceftazidime-avibactam plus aztreonam in clinical instability, intolerance, or resistance to other alternatives.	In patients with infections resistant to TMP-SMX or if it cannot be used, perform combined treatment based on *in vitro* activity.
Use TMP-SMX 8-12mg/kg (TMP) in combination therapy, at least until clinical improvement.	Use TMP-SMX at 15mg/Kg/day (TMP) in 3-4 doses adjusted to renal function.
High doses of minocycline (200mg/12h) in combination therapy is reasonable, until clinical improvement. Tigecycline is a sensible option.	Levofloxacin monotherapy is non-inferior to TMP-SMX monotherapy. If fluoroquinolones are used, emergence of resistance during treatment may appear.
We recommend cefiderocol in combined therapy until clinical improvement.	In patients with limited options consider second-line agents based on *in vitro* test.
Use levofloxacin as part of combination therapy. It is not advised leave it on monotherapy after clinical improvement.	

potential for on-treatment resistance development currently appears to be low, although more clinical data are required. Information from surveillance programs, real-world compassionate use, and clinical studies demonstrate that cefiderocol is an important treatment option for MBL-producing *P. aeruginosa* infections, including pneumonia [140,173–175].

Acinetobacter baumannii* and *Stenotrophomonas maltophilia. *A. baumannii complex* and *S. maltophilia* are two opportunistic bacterial species that cause nosocomial infection (mainly HAP-VAP and bacteraemia). *A. baumannii* is associated with resistance mechanisms that the World Health Organization (WHO) introduced in the "*WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria*" (Priority 1: critical) [176]. Especially in HAP-VAP infections, combinations of ampicillin-sulbactam together with cefiderocol, tigecycline or colistin have been proposed to increase the probability of therapeutic success [177]. IDSA and ESCMID recommendations in high-risk and severe ill patients suggest the combination of at least of two antibiotics with *in vitro* activity. Table 10 shows the differences between the recommendations for treatment of *A. baumannii* Carbapenems Resistant (CR) provided by IDSA and ESCMID [163,177,178]. Among the future options, it is worth highlighting the trials that are being carried out with sulbactam/durlobactam.

Infections caused by the opportunistic pathogen *S. maltophilia* in immunocompromised patients are complicated to treat due to antibiotic resistance and the ability of the bacteria to produce biofilm [179]. These bacteria colonize the surface of medical devices such as urinary catheters, endoscopes, and ventilators; they can cause respiratory tract infections. Low outer membrane permeability due to multidrug-resistant efflux systems and the two chromosomally encoded β-lactamases present are a challenge for antimicrobial treatment. Moreover, there is a wide spread of antibiotic resistance genes among *S. maltophilia* that contribute to enhanced resistance to multiple antibiotics, such as penicillin, quinolones, and carbapenems. Nevertheless, tetracycline derivatives, fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX) and cefiderocol are considered promising antibiotics. Due to the adaptive nature of the intrinsically resistant mechanism and its ability to acquire new resistance via mutation and horizontal gene transfer, it remains a challenge for clinicians [179,180]. The combination of ceftazidime-avibactam plus aztreonam could be a good option when there is resistance to TMP-SMX and fluoroquinolones [181]. Table 11 displays the differences between the recommendations for treatment of *S. maltophilia* treatment provided by IDSA and ESCMID [163,178,182].

Current debates in respiratory sepsis

Steroids. Role of corticosteroids in severe pneumonia is controversial, as available evidence suggests [183–185]. In severe viral respiratory infections, causing pathogen is an important issue. As previously it has been mentioned, severe influenza pneumonia does not benefit from corticosteroid treatment [186], whereas dexamethasone is a corner stone for treatment of severe COVID-19 pneumonia [30]. However, some unanswered questions persist about the effectiveness of corticosteroids for this last entity. There is contradictory evidence about reduction of mortality in ventilated patients. A retrospective study of prospectively collected data conducted in 70 ICUs (mainly Spanish), included mechanically ventilated COVID-19-associated acute respiratory distress syndrome (ARDS) patients admitted in 2020. Patients exposed to corticosteroids at admission were matched with patients without, through propensity score matching. Primary outcome was all-cause ICU mortality. Secondary outcomes were to compare in-hospital mortality, ventilator-free days at 28 days, respiratory superinfection, and length of stay between them. ICU mortality did not differ between patients treated with and without corticosteroids and untreated patients. In survival analysis, corticosteroid treatment at ICU admission was associated with short-term survival benefit (HR 0.53; 95% CI 0.39–0.72), although beyond

the 17th day of admission, this effect switched and there was an increased ICU mortality (long-term HR 1.68; 95% CI 1.16–2.45). The sensitivity analysis reinforced the results. Subgroups of age less of 60 years, severe ARDS and corticosteroids plus tocilizumab could have greatest benefit from corticosteroids. Short-term courses of corticosteroids decreased ICU mortality without long-term negative effects. Longer length of stay was observed with corticosteroids among non-survivors both in the ICU and in hospital. There were no significant differences for the remaining secondary outcomes [187]. So, it seems that long term treatment of corticosteroid in ICU does not give any benefit.

CAP requiring intensive care unit admission, as it was previously mentioned, is associated with significant acute and long-term morbidity and mortality. Some papers support it use [27,184], whereas others show lack of benefit [31,185,188,189]. Recently, hydrocortisone has shown utility in a randomized clinical trial, but it only showed benefit in patients with spontaneous ventilation, unknown microorganism, younger than 65 years, women, milder pneumonia, and patients with strong inflammatory reaction -C reactive protein more than 15 mg/dL- [27]. So, patient's phenotype plays an important role to reach benefit from corticosteroid therapy in severe CAP [31,190].

Some meta-analyses have been performed to try to solve this question, but they lack enough validity due to risk of bias or because they included too old studies [191–195]. It seems that corticosteroid can aid to avoid death in patients in ICU with septic shock [196].

The controversy over the impact of corticosteroids on CAP still persists. The limitations of the studies and meta-analyses do not allow us to give a definitive answer. New machine learning techniques might resolve this controversy, which may allow evaluating the impact of corticosteroids according to different clinical phenotypes based on large real-life databases [197–199].

Use of vasoactive amines. Sepsis is an organic dysfunction caused by a dysregulated patient's answer to infection and it can cause death. Sepsis and septic shock are important and prevalent health issues worldwide and they kill between one and three of each six affected patients. Sepsis caused death of 11 million people in 2017, which is 20% of total worldwide mortality. Early identification and proper management in first hours are key to improve outcomes. The main priority is to correct hypoperfusion [200,201].

Current guidelines recommend offering 30 mL/kg of intravenous crystalloid within the first three hours, with a low quality of evidence. They also recommend considering additional fluids which must be guided by frequent reassessment of hemodynamic status [201]. However, there is a risk of under or over-resuscitation in some patients, so alternative approaches have been proposed. To offer 10 mL/kg of intravenous crystalloid within first hour seems a safer method. After this, a revaluation of the patient must be done to assess signs of hypovolemia or congestion and to tailor therapy to those signs [202].

Objectives of hemodynamic reanimation are to assure an adequate perfusion pression and to correct hypoperfusion data [203], as can be seen in Figure 3. Mean arterial pressure (MAP) objective is 65 mmHg. Higher objectives, such as 85 mmHg, increase risk of atrial fibrillation, but in patients with previous chronic hypertension this objective can reduce rate of use of renal replacement therapies [204]. Early use of vasopressors is advised to achieve this personalized objective. Norepinephrine is the first choice because it potentiates the efficacy of volume expansion, and it is associated with lower mortality, shorter time to achieve target MAP and less volume of intravenous fluids [205,206]. Dose of norepinephrine must be tailored to patient's response until doses between 0.25-0.5 µg/Kg/min. Norepinephrine perfusion can be delivered by a peripheric venous access, such as a vein in antecubital fossa with a wide catheter (number 18 or wider). This approach allows to begin with vasopressor administration earlier until a central venous access is secured [201,207]. Although norepinephrine is the preferred option to achieve MAP objective in septic shock, there are other drugs with different profiles of effects over adrenergic and other vascular wall and heart receptors [208]. There is strong evidence against use of dopamine in septic shock because it is associated with higher mortality and risk of arrhythmias [209].

If objective MAP is not achieved despite an adequate fluid resuscitation and optimized norepinephrine perfusion, guidelines recommend adding vasopressin (0.01 – 0.03 U/min, fixed dose) instead of increasing norepinephrine doses. In case this combination is not enough, epinephrine must be considered. Also, corticosteroids can be employed if hypotension persists. Terlipressin must be avoided because it increases risk of peripheral and mesenteric ischemia. End of vasoactive drug perfusion may be considered if patient is stable and without hypoperfusion signs for at least six hours, and catecholamines are the first drugs to be progressively withdrawn [201].

Patients with myocardial disfunction will also need inotropes. There are two choices: to use a combination of dobutamine and norepinephrine or epinephrine alone. Neither has demonstrate superiority over the other option, but the employment of dobutamine and norepinephrine allows to adjust each drug independently from the other and prevents potential lactic acidosis produced by epinephrine [201]. Levosimendan is associated with higher frequency of supraventricular tachyarrhythmias and lower rates of successful weaning from mechanical ventilation, so it must be avoided [210].

These facts are summarized in an algorithm (Figure 3). As can be seen, therapy must be tailored to patient's characteristics and response to therapies. A personalized approach is key to get best results.

Ventilatory support. Severe pneumonia is a leading cause of acute respiratory distress syndrome -ARDS-. Classic definition of ARDS attends only to relationship between oxygen arterial partial pression and oxygen inspired fraction -PAFI- [211]. Emerging evidence in recent years, as well as the experience with the COVID-19 pandemic, have made evident the need for other parameters in addition to PAFI to adapt ventilatory

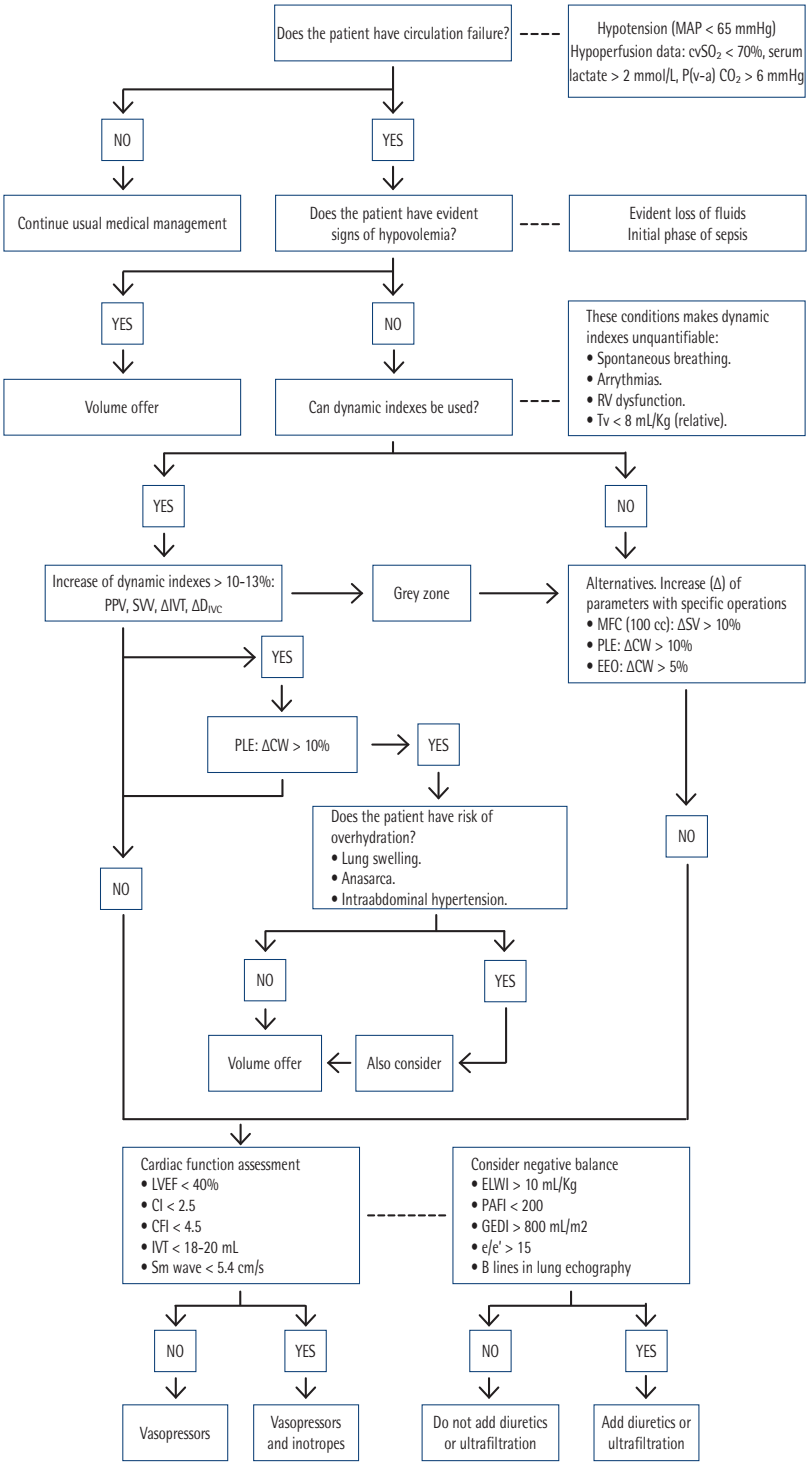

Figure 3 | **Algorithm of hemodynamic management.**

MAP: mean arterial pressure, $cvSO_2$: central venous oxygen saturation, $P(v\text{-}a)CO_2$: partial pression veno-arterial of CO_2, Tv: tidal volume, PPV: pulse pression variation, SVV: systolic volume variation, IVT: integral of velocity with respect to left ventricular outflow tract flow, DIVC: inferior vein cava diameter, MFC: mini-fluid challenge, PLE: passive leg elevation, EEO: end-expiratory occlusion, SV: systolic volume, CW: cardiac waste, LVEF: left ventricle ejection fraction, CI: cardiac index, CFI: cardiac function index, ELWI: extravascular lung water index, GEDI: global end-diastolic global volume index, PAFI: relationship between oxygen arterial partial pression and oxygen inspired fraction, e/e': echocardiogram e/e' index.

support to patients with ARDS [212]. In fact, a great variability in mortality between different ICU services was observed during COVID-19 pandemic. These variations were attributed to heterogeneous organization and level of training, early use of respiratory support and prevention of secondary infections [213]. It also showed importance of longitudinal assessment of patients. Several phenotypes were recognized in patients with COVID-19, and an increase of dead space and mechanical power were associated with poorer prognosis [214]. Precision medicine, along with tailored therapies to single characteristics of each patient, has been recognized as an important requirement to improve outcomes in intensive care. To realise this, it is necessary an exhaustive monitoring and data-driven decision-making [215]. Current guidelines recognize importance of different phenotypes based on systemic inflammatory response, lung radiographic morphology, clinical features, and longitudinal changes in respiratory parameters; but they are not very flexible, and they lack enough detailed recommendations to tackle these longitudinal evolutionary changes [216]. The identification of these phenotypes may allow better outcomes. It is also important to recognize ARDS in illness that do not affect lungs primarily, because in these cases a delayed diagnosis is frequent [216,217]. Moreover, in non-invasive approaches, election of interface is very important. For example, in COVID-19 pandemic, continuous positive airway pressure -CPAP- was better than high flow nasal oxygen -HFNO- [218].

A protective strategy to perform invasive mechanical ventilation is key to prevent harm derived of medical procedures and to improve clinical results. Periodical evaluations are needed to tailor ventilatory parameters to patient's evolution. Common mistakes to avoid are [219]: Breath-stacking or expiratory dysynchrony, excessive or insufficient ventilator assistance, excessive or insufficient sedation and excessive or insufficient PEEP (positive end-expiratory pressure).

Finally, considering these concepts, a unified approach is proposed to treat patients with ARDS (Figure 4).

Extracorporeal membrane oxygenation (ECMO). ECMO provides circulatory (venous and/or arterial) and/or respiratory support for a short period of time (days or weeks) in patients with cardiac or respiratory failure refractory to conventional treatments [220]. Clinicians can indicate ECMO in these settings when all other available treatments fail [220]: Pneumonia of any aetiology, aspiration syndromes, alveolar proteinosis, obstetric pathology, inhalation syndromes, airway obstruction, pulmonary contusion, bronchopleural fistula, bridge therapy, intraoperative respiratory support, asthmatic status, pulmonary haemorrhage or massive haemoptysis, hypercapnia (pH < 7.20) and/or $PaCO_2$ > 80 mmHg, inability to maintain plateau pressure < 30 cmH_2O, pulmonary vasculitis.

ECMO contraindications in ARDS are [220]: lung disease without predictable recovery of lung function if lung transplant is not indicated, contraindications for anticoagulation treatment, age > 65 years (more limited evidence). It is a relative contraindication, multiorgan failure with SOFA > 15 points, mechanical ventilation more than 7 days (special consideration with plateau pressure >30 cmH_2O, impossibility of pressure>10 mmH_2O, FiO_2 > 0.9). It is a relative contraindication, severe pharmacological immunosuppression (neutrophils < 400/mm^3), coma after cardiac arrest, comorbidities (active malignant disease, obesity, chronic heart disease, non-transplantable lung disease, cirrhosis with ascites, irreversible neurological disease), haemorrhagic or potentially haemorrhagic central nervous system lesions, impossible cannulation.

Patients with severe bacterial pneumonia can benefit from this technique [221,222] and it also has demonstrated utility in severe COVID-19 [223–225].

Although it is a live saving procedure for severe ill patients, it is associated with potential lethal complications such as catheter-related bacteraemia (14-44 ‰ catheter days), VAP (20-60‰ days of ventilation), catheter-related urinary tract infection (1-14‰ days of catheterization) and it also affects the pharmacokinetics and pharmacodynamics of some drugs (for example lipophilic drugs) [220,226–231]. In Spain, nosocomial infections were more frequent in patients with COVID-19 pneumonia [226]. Moreover, diagnosis of infectious complications is difficult due to frequent absence of fever, blood dyscrasias caused by technique and hypotension. Biomarkers, such as procalcitonin and lactate, are useful to recognize infectious complications [232].

Nowadays, ECMO could be consider as an essential technique that contributes to improving the patient's condition with refractory SDRA for clinical recovery.

Approach to fungal pneumonia

Pneumonia by *Pneumocystis jirovecii* in patients without human immunodeficiency virus (HIV). *P. jirovecii* pneumonia (PJP) in patients without HIV infection is an important problem to clinicians nowadays. Its prevalence is rising because there is a growing number of vulnerable patients each year, diagnosis is usually delayed because of low grade of suspicion and, therefore, mortality is higher than in patients with HIV infection [233]. Risk factors for developing PJP are [119,234–237]:

- Acute lymphoblastic leukaemia.
- Allogenic stem cell transplant.
- Solid organ transplant. In those patients, PJP usually develops in the first two months from transplant. Additional risk factors for those patients are age more than 65 years, CMV infection in the year preceding the transplant, immunosuppressive therapy containing tacrolimus and lymphopenia in the 50 days prior to transplant (<750 mm^3).
- Autologous stem cell transplant for underlying hematologic malignancy.
- Chimeric antigen receptor-modified T-cell therapy.
- Primary immunodeficiency: severe combined immunodeficiency, idiopathic CD4 T-lymphopenia, hyper IgM syndrome.

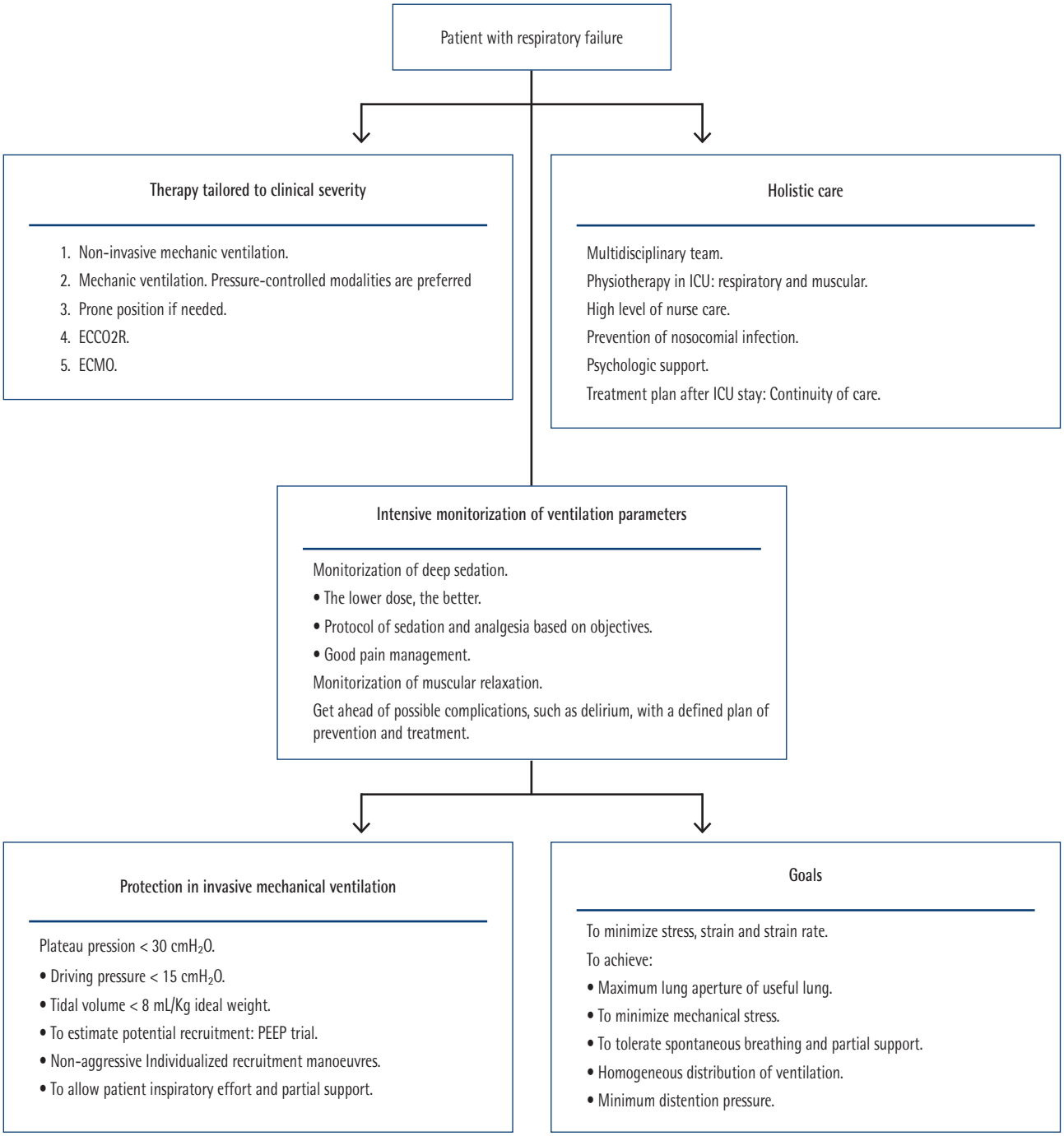

Figure 4 | **Unified approach to treat ARDS.**

ECCO2R: extracorporeal carbon dioxide removal. ECMO: extracorporeal membrane oxygenation. PEEP: positive end-expiratory pressure.

- Patients receiving high-dose corticosteroid treatment (equivalent to 20 mg or more of prednisone daily for more than one month) who have additional cause of immunodeficiency, such as malignancy or additional immunosuppressive medications.
- Patients with COVID-19 and low count of lymphocytes, prior immunosuppression, more days of illness, high doses of corticosteroids or long courses of them.
- Other immunosuppressive therapies, such as anti-CD20 monoclonal antibody, cytotoxic chemotherapy, mTOR inhibition, calcineurin inhibition, phosphatidylinositol 3-kinase inhibition, etc.
- Previous episode of PJP.

Although there is not a complete consensus for all these groups of patients, they should take PJP chemoprophylaxis, usually with low dose of trimethoprim-sulfamethoxazole (e.g. 800/160 mg by mouth thrice a week) [119,234].

Patients with PJP usually suffer from sudden shortness of breath with respiratory failure, non-productive cough, and fever. They also have serum lactate-dehydrogenase (LDH) levels higher than patients with PCP and HIV. Chest X-ray can be initially normal or with interstitial infiltrates. Traditional microbiological methods for diagnosis are special staining of respiratory samples (toluidine blue, Giemsa, silver-methenamine) and immunofluorescence. This last one, made in BAL sample, is considered gold-standard test. Recently, molecular techniques such as PCR of respiratory specimens and detection of β-D-glucan in serum are available [233]. However, it is necessary to facilitate the diagnosis, so innovative approaches have been developed in last years:

- Detection of *P. jirovecii* by molecular techniques (PCR) in oral wash samples in immunocompromised patients or nasopharyngeal swabs. Both methods have a high negative predictive value (NPV) near to 100%, but a lower positive predictive value -70-80%- [238,239].
- PCR in respiratory samples is an extremely sensitive technique, so it is vulnerable to false positives. Cycle threshold (Ct) is useful to distinguish false from true positives. Lower Ct -less than 30- is associated with illness, whereas higher Ct -more than 35- is associated with colonization [240].

Detection of high serum concentration of β-D-glucan (>200 pg/mL with Fungitell®) is correlated with likelihood of illness in oncologic patients, and it has a high negative predictive value in patients with negative PCR [241].

There are several commercial kits to detect β-D-glucan in serum, with different thresholds. Serum levels associated with PCP are higher than the ones registered with candidemia [242].

This emerging knowledge can be summarized as [241,243–246]: Immunofluorescence performed in BAL remains gold-standard test. Immunofluorescence stains made in induced sputum is also accepted as diagnostic proof of PJP. In patients unable to endure a bronchoscopy, serum β-D-glucan has a high NPV that allows rule-out PJP in patients with low to moderate grade of suspicion. In fact, Bigot et al propose to do this test prior to bronchoscopy and to avoid it if test result is negative [245]. Patients with high grade of suspicion may need molecular techniques in respiratory samples. In patients with both negative tests, PCP is very unlikely. If both tests are positive, PCP is probable. Finally, in patients with serum positive β-D-glucan and negative PCR in respiratory sample, it must be reconsidered to perform a bronchoscopy and other fungal infections should be discarded.

These concepts are aligned with the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSEGERC) consensus to define invasive fungal disease [247]. Host factors -immunosuppression-, clinical criteria -symptoms, signs, and radiological findings -, and microbiologic criteria must be fulfilled to achieve a diagnosis. According to the degree of certainty, two categories can be distinguished:

- Proven PCP. Patient with clinical and radiological criteria, who also has a positive immunofluorescence staining in tissue or respiratory sample.

Probable PCP. Patient with predisposing host factors, clinical and radiological criteria who also has a positive molecular technique in respiratory specimens or positive detection of β-D-glucan. In this last scenario, clinicians should have a high grade of suspicion for another invasive fungal infection, because it could be a false positive.

As it has been shown, there is still some uncertainty to make a sure diagnosis of PCP. Novel approaches such as detecting circulating DNA of *P. jirovecii* in serum and machine learning tools have been demonstrated itself promising and their routine employment may be near [248,249].

Despite new diagnostic tools developed in last years, treatment of PCP has remained without changes and high dose of trimethoprim-sulfamethoxazole (15 mg/kg/d iv) continues being treatment of choice for most patients [119]. However, this high dose is often associated with negative adverse events which can be treatment limiting, so a clinical trial is nowadays active to compare standard dose with low dose (10 mg/kg/d) [250]. In patients not infected with HIV, the use of corticosteroids in moderate-severe pneumonia with hypoxemia remains controversial.

Invasive aspergillosis. The clinical presentation of aspergillosis lung disease is determined by the interaction between fungus (*Aspergillus* spp., with their virulence factors and/or resistance to antifungals) and their host (generally dependent on its immune status and previous structural bronchopulmonary local involvement). Invasive pulmonary aspergillosis (IPA) develops in severely immunocompromised patients, such as onco-haematology patients -especially those with neutropenia-, and its incidence is rising in the non-neutropenic, including lung transplant recipients, the critically ill patients and patients on corticosteroid treatment [251].

A high index of suspicion is required in patients without the typical risk factors (severe and prolonged neutropenia, HIV infection, high dose steroids, cirrhosis, alteration of

T lymphocyte function, acute myeloid leukaemia, and allogeneic hematopoietic cell transplantation) as early presentation is usually silent and non-specific and pyrexia is uncommon. This high index of suspicion is very important because timely treatment is crucial for survival. Recently, acute viral infections have been associated with IPA leading to the concepts of influenza-associated IPA (IAPA) and COVID-19-associated IPA (CAPA) [251,252]. These viral infections may affect patients without underlying disease. Invasive aspergillosis has also been diagnosed in normal hosts after massive exposure to fungal spores (mainly *A. fumigatus*). Chronic pulmonary aspergillosis affects patients without obvious immune compromise, but with an underlying lung condition such as chronic obstructive pulmonary disease (COPD) or sarcoidosis, prior or concurrent tuberculous or non-tuberculous mycobacterial disease [252–254]. An invasive form of aspergillosis is seen in lung and heart transplant recipients that involves the trachea and bronchi, and in particular, the bronchial anasthosmosis.. Asymptomatic colonisation of the respiratory tract needs close monitoring as it can lead to clinical disease especially with future immunosuppression [253,254]. The halo sign is the radiological representation of lung infarction that follows angioinvasion by hyphae. The nodule represents the coagulation necrosis, and the halo is the oedema and haemorrhage that surround the zone of infarction. Although not specific, its presence in persistently febrile neutropenic patients must be interpreted as suggestive of an invasive disease. An important contribution to the management of IPA was made by studies showing the importance of the halo sign as the earliest detectable mark of disease [252].

Several tests are available for the diagnosis of IPA mainly in two types of clinical sample: BAL and serum. In both of them, specific PCR, lateral flow device, determination of β-1-3 D-glucan and galactomannan can be performed. In BAL samples the culture could be recommended to study susceptibility. [254].

Currently, there is not scientific evidence to support the superiority of one antifungal over another for the treatment of CAPA/IAPA. Therefore, it is recommended to follow the treatment indications in current national and international guidelines, considering the peculiarities of critical patients and, in particular, of patients with severe viral pneumonia due to influenza or COVID-19 [253,254]. It is recommended to include voriconazole, isavuconazole or liposomal amphotericin B as first-line drugs for the treatment of CAPA/IAPA patients. Surgery must be considered in case of great vessel affectation or massive haemoptysis. The antifungal treatment of CAPA/IAPA patients is recommended until diagnosis is confirmed [254]. New antifungal could be in the future therapeutic arsenal to treat *Aspergillus* spp. resistant isolates such as fosmanogepix, olorofim, opelconazol, ibrexafungerp and rezafungin [255,256].

CONCLUSIONS

Targeted treatment has always been a great challenge in planning clinical work algorithms, especially in sepsis with respiratory origin or HAP/VAP. Molecular biology techniques in microbiology could contribute to obtain quicker results to achieve therapeutic success. New documents that give answers to important questions about CAP, HAP, and VAP are available. Interdisciplinary teams generate knowledge that might improve clinical results. Beta-lactam allergy in patients with pneumonia is associated with worse outcomes due to therapeutical limitations. False label of beta-lactam allergy must be removed as soon as possible, and profile of hypersensitivity must be defined to allow use of beta-lactam antibiotics which lack of cross-reactions in a particular patient. Multidisciplinary projects such as Zero Pneumonia are useful to prevent VAP. Severe CAP is a main cause of mortality despite efforts done in last decades. A timely approach is essential to change this, and a tailored use of antibiotics may help to achieve better endings. Sequential therapy is strongly recommended to treat pneumonia, because it is a safe alternative and is associated with lower cost and length of stay than exclusive intravenous therapy. Several options are available. Alternatives currently available in MBL-producing *P. aeruginosa* isolates are: cefiderocol, aztreonam-avibactam, high doses of amikacin and synergistic combinations tailored to antibiotic *in vitro* test results, including fosfomycin, colistin or others, systemically and/or nebulized. New beta-lactam antibiotics are available to treat HAP and VAP, with better outcomes than older alternatives. A personalized approach must be employed to choose the best empiric treatment available, and clinicians must bear in mind specific patient profile, local epidemiology, and results of stains and molecular methods such as PCR. Nebulized antibiotics are not recommended for treatment, whereas they may be useful for prophylaxis of VAP. Ceftazidime-avibactam, meropenem-vaborbactam and cefiderocol are current alternatives in the treatment of HAP-VAP caused by non-MBL CRE, especially carbapenemases OXA-48 like and KPC types. *A. baumannii complex* and *S. maltophilia* are two opportunistic bacterial species that cause nosocomial infection (mainly HAP-VAP and bacteraemia). The IDSA and ESCMID recommendations could be of help to elaborate an individualized treatment in multi-resistant isolates. The controversy over the impact of corticosteroids on CAP still persists. It can be resolved by applying new machine learning techniques that could identify phenotypes that benefit from this treatment. Sepsis and septic shock are illness with a high associated prevalence and mortality. Early correction of hypoperfusion with intravenous fluids and promptly vasoactive therapy can enhance patient's results. An adapted therapy to patients with severe pneumonia and respiratory failure might improve clinical results. A holistic approach and intensive monitorization allow get ahead of potential problems. ECMO provides circulatory and/or respiratory support for patients with refractory SDRA. It allows patients to heal when other methods are ineffective. In fungal world, IPA caused by *Aspergillus* spp remains a great challenge in the ICU for both its diagnosis and treatment, in part due to the difficulty of differentiating between colonization and infection.

PCP in patients without HIV infection is an illness that affects immunosuppressed patients. Its diagnosis is difficult and requires a high grade of suspicion. Consequently, late diagnosis is often performed, and prognosis is poorer than in patients with HIV. New diagnostic approaches, such as PCR in respiratory samples and detection of β-D-glucan in serum, may allow an earlier diagnosis. High doses of trimethoprim -sulfamethoxazole remain best treatment available. Prevention is key, so selected patients with predisposing conditions, some belonging to new risk groups, should receive chemoprophylaxis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, et al. Pneumonia. Nat Rev Dis Primers. 2021 Apr 8;7(1):25.
2. Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis [Internet]. 2017 Nov 10;36(11):1999–2006. Available from: http://link.springer.com/10.1007/s10096-016-2703-z
3. Metersky ML, Wang Y, Klompas M, Eckenrode S, Bakullari A, Eldridge N. Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013. JAMA. 2016 Dec 13;316(22):2427.
4. Cillóniz C, Dominedò C, Torres A. An overview of guidelines for the management of hospital-acquired and ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria. Curr Opin Infect Dis. 2019 Dec;32(6):656–62.
5. Dominedò C, Ceccato A, Niederman M, Cillóniz C, Gabarrús A, Martin-Loeches I, et al. Predictive Performance of Risk Factors for Multidrug-Resistant Pathogens in Nosocomial Pneumonia. Ann Am Thorac Soc. 2021 May;18(5):807–14.
6. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J. 2017 Sep 10;50(3):1700582.
7. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):575–82.
8. Torres A, Barberán J, Ceccato A, Martin-Loeches I, Ferrer M, Menéndez R, et al. Neumonía intrahospitalaria. Normativa de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Actualización 2020. Arch Bronconeumol. 2020 Mar;56:11–9.
9. Erb CT, Patel B, Orr JE, Bice T, Richards JB, Metersky ML, et al. Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia. Ann Am Thorac Soc. 2016 Dec;13(12):2258–60.
10. Bassetti M, Righi E, Vena A, Graziano E, Russo A, Peghin M. Risk stratification and treatment of ICU-acquired pneumonia caused by multidrug- resistant/extensively drug-resistant/pandrug-resistant bacteria. Curr Opin Crit Care. 2018 Oct;24(5):385–93.
11. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia. Curr Opin Pulm Med. 2013 May;19(3):216–28.
12. Vacas-Córdoba M, Cardozo-Espinola C, Puerta-Alcalde P, Cilloniz C, Torres A, García-Vidal C. Empirical treatment of adults with hospital-acquired pneumonia: lights and shadows of the 2016 Clinical Practice ATS/IDSA Guidelines. Rev Esp Quimioter. 2017 Sep;30 Suppl 1:30–3.
13. Vallés J, Martin-Loeches I, Torres A, Diaz E, Seijas I, López MJ, et al. Epidemiology, antibiotic therapy and clinical outcomes of healthcare-associated pneumonia in critically ill patients: a Spanish cohort study. Intensive Care Med. 2014 Apr 18;40(4):572–81.

14. GEIPC-SEIMC. V Jornada Anual de Neumonía [Internet]. 2023 [cited 2023 Dec 8]. Available from: https://jornada-anual-neumonia.com/
15. Kollef MH, Shorr AF, Bassetti M, Timsit JF, Micek ST, Michelson AP, et al. Timing of antibiotic therapy in the ICU. Crit Care. 2021;25(1):360.
16. Casey JD, Beskow LM, Brown J, Brown SM, Gayat É, Ng Gong M, et al. Use of pragmatic and explanatory trial designs in acute care research: lessons from COVID-19. Lancet Respir Med. 2022 Jul;10(7):700–14.
17. Candel FJ, Salavert M, Basaras M, Borges M, Cantón R, Cercenado E, et al. Ten Issues for Updating in Community-Acquired Pneumonia: An Expert Review. J Clin Med. 2023 Oct 30;12(21):6864.
18. Candel FJ, Salavert M, Estella A, Ferrer M, Ferrer R, Gamazo JJ, et al. Ten Issues to Update in Nosocomial or Hospital-Acquired Pneumonia: An Expert Review. J Clin Med. 2023 Oct 14;12(20):6526.
19. Caméléna F, Péan de Ponfilly G, Pailhoriès H, Bonzon L, Alanio A, Poncin T, et al. Multicenter Evaluation of the FilmArray Blood Culture Identification 2 Panel for Pathogen Detection in Bloodstream Infections. Microbiol Spectr. 2023 Feb 14;11(1).
20. Serigstad S, Markussen D, Grewal HMS, Ebbesen M, Kommedal Ø, Heggelund L, et al. Rapid syndromic PCR testing in patients with respiratory tract infections reduces time to results and improves microbial yield. Sci Rep. 2022 Jan 10;12(1):326.
21. Gadsby NJ, Musher DM. The Microbial Etiology of Community-Acquired Pneumonia in Adults: from Classical Bacteriology to Host Transcriptional Signatures. Clin Microbiol Rev. 2022 Dec 21;35(4):e0001522.
22. Serigstad S, Markussen DL, Ritz C, Ebbesen MH, Knoop ST, Kommedal Ø, et al. The changing spectrum of microbial aetiology of respiratory tract infections in hospitalized patients before and during the COVID-19 pandemic. BMC Infect Dis. 2022 Sep 30;22(1):763.
23. Gentilotti E, De Nardo P, Cremonini E, Górska A, Mazzaferri F, Canziani LM, et al. Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections. A systematic review and meta-analysis. Clin Microbiol Infect. 2022 Jan;28(1):13–22.
24. Bellew S, Grijalva CG, Williams DJ, Anderson EJ, Wunderink RG, Zhu Y, et al. Pneumococcal and Legionella Urinary Antigen Tests in Community-acquired Pneumonia: Prospective Evaluation of Indications for Testing. Clin Infect Dis. 2019 May 30;68(12):2026–33.
25. Kim P, Deshpande A, Rothberg MB. Urinary Antigen Testing for Respiratory Infections: Current Perspectives on Utility and Limitations. Infect Drug Resist. 2022 Apr;Volume 15:2219–28.
26. Wick KD, McAuley DF, Levitt JE, Beitler JR, Annane D, Riviello ED, et al. Promises and challenges of personalized medicine to guide ARDS therapy. Crit Care. 2021 Dec 23;25(1):404.
27. Dequin PF, Meziani F, Quenot JP, Kamel T, Ricard JD, Badie J, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023 May 25;388(21):1931–41.
28. Nedel WL. Corticosteroids for severe influenza pneumonia: A critical appraisal. World J Crit Care Med. 2016;5(1):89.
29. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45–67.
30. The RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med . 2021 Feb 25;384(8):693–704.
31. Moreno G, Ruiz-Botella M, Martín-Loeches I, Gómez Álvarez J, Jiménez Herrera M, Bodí M, et al. A differential therapeutic consideration for use of corticosteroids according to established COVID-19 clinical phenotypes in critically ill patients. Med Intensiva. 2023 Jan;47(1):23–33.
32. Menéndez R, Cilloniz C, España PP, Almirall J, Uranga A, Méndez R, et al. Neumonía adquirida en la comunidad. Normativa de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Actualización 2020. Arch Bronconeumol. 2020 Mar;56:1–10.
33. Capelastegui A, España Yandiola PP, Quintana JM, Bilbao A, Diez R, Pascual S, et al. Predictors of Short-term Rehospitalization Following Discharge of Patients Hospitalized With Community-Acquired Pneumonia. Chest. 2009 Oct;136(4):1079–85.
34. Jang JG, Ahn JH. Reasons and Risk Factors for Readmission Following Hospitalization for Community-acquired Pneumonia in South Korea. Tuberc Respir Dis (Seoul). 2020;83(2):147.
35. Mather JF, Fortunato GJ, Ash JL, Davis MJ, Kumar A. Prediction of Pneumonia 30-Day Readmissions: A Single-Center Attempt to Increase Model Performance. Respir Care. 2014 Feb;59(2):199–208.
36. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Diagnoses and Timing of 30-Day Readmissions After Hospitalization for Heart Failure, Acute Myocardial Infarction, or Pneumonia. JAMA. 2013 Jan 23;309(4):355.
37. Nguyen DT, Huynh ST, Nguyen HN. Short-Term Readmission Following Community-Acquired Pneumonia: A Cross-Sectional Study. Hosp Pharm. 2022 Dec 25;57(6):712–20.
38. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on Hospital Discharge and the Risk of Adverse Outcomes in Patients With Pneumonia. Arch Intern Med. 2002 Jun 10;162(11):1278.
39. Fleuren LM, Klausch TLT, Zwager CL, Schoonmade LJ, Guo T, Roggeveen LF, et al. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med. 2020 Mar 21;46(3):383–400.
40. Quah J, Liew CJY, Zou L, Koh XH, Alsuwaigh R, Narayan V, et al. Chest radiograph-based artificial intelligence predictive model for mortality in community-acquired pneumonia. BMJ Open Respir Res. 2021 Aug 9;8(1):e001045.
41. Akarapipad P, Bertelson E, Pessell A, Wang TH, Hsieh K. Emerging Multiplex Nucleic Acid Diagnostic Tests for Combating COVID-19. Biosensors (Basel). 2022 Nov 7;12(11):978.
42. Leber AL, Everhart K, Daly JA, Hopper A, Harrington A, Schreckenberger P, et al. Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples. J Clin Microbiol. 2018 Jun;56(6).
43. Lee SH, Ruan SY, Pan SC, Lee TF, Chien JY, Hsueh PR. Performance

of a multiplex PCR pneumonia panel for the identification of respiratory pathogens and the main determinants of resistance from the lower respiratory tract specimens of adult patients in intensive care units. J Microbiol Immunol Infect. 2019 Dec;52(6):920–8.

44. Gibson J, Schechter-Perkins EM, Mitchell P, Mace S, Tian Y, Williams K, et al. Multi-center evaluation of the cobas ® Liat ® Influenza A/B & RSV assay for rapid point of care diagnosis. J Clin Virol. 2017 Oct;95:5–9.
45. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45–67.
46. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):575–82.
47. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J. 2017 Sep 10;50(3):1700582.
48. Estella A. [Analysis of 208 flexible bronchoscopies performed in an intensive care unit]. Med Intensiva. 2012;36(6):396–401.
49. Fujitani S, Yu VL. Diagnosis of Ventilator-Associated Pneumonia: Focus on Nonbronchoscopic Techniques (Nonbronchoscopic Bronchoalveolar Lavage, Including Mini-BAL, Blinded Protected Specimen Brush, and Blinded Bronchial Sampling) and Endotracheal Aspirates. J Intensive Care Med. 2006 Jan 30;21(1):17–21.
50. Morris AC, Kefala K, Simpson AJ, Wilkinson TS, Everingham K, Kerslake D, et al. Evaluation of the effect of diagnostic methodology on the reported incidence of ventilator-associated pneumonia. Thorax. 2009 Jun 1;64(6):516–22.
51. Flanagan PG, Findlay GP, Magee JT, Ionescu A, Barnes RA, Smithies M. The diagnosis of ventilator-associated pneumonia using non-bronchoscopic, non-directed lung lavages. Intensive Care Med. 2000 Jan;26(1):20–30.
52. Zaragoza R, Vidal-Cortés P, Aguilar G, Borges M, Diaz E, Ferrer R, et al. Update of the treatment of nosocomial pneumonia in the ICU. Crit Care. 2020 Jun 29;24(1):383.
53. González Ramallo VJ, Mirón Rubio M, Estrada Cuxart O, García Leoni ME. Usefulness of Hospital at Home in nosocomial infections: advantages and limitations. Rev Esp Quimioter. 2017 Sep;30 Suppl 1:61–5.
54. Mujal A, Sola J, Hernandez M, Villarino MA, Machado ML, Baylina M, et al. Safety and effectiveness of home intravenous antibiotic therapy for multidrug-resistant bacterial infections. Eur J Clin Microbiol Infect Dis. 2015 Jun 6;34(6):1125–33.
55. Esteban-Cartelle B, Vicente-Oliveros N, Pérez Menéndez-Conde C, Serrano DR, Martín-Dávila P, Fortún-Abete J, et al. Antibiotic stability in portable elastomeric infusion devices: A systematic review. Am J Health Syst Pharm. 2022 Aug 5;79(16):1355–68.
56. Paño-Pardo JR, Moreno Rodilla E, Cobo Sacristan S, Cubero Saldaña JL, Periañez Párraga L, del Pozo JL, et al. Management of patients with suspected or confirmed antibiotic allergy. Executive summary of guidance from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Allergy and Clinical Immunology (SEAIC), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society of Intensive Medicine and Coronary Care Units (SEMICYUC). Enferm Infecc Microbiol Clin. 2023 Mar;41(3):181–6.
57. Muñoz Román C, Vilá Indurain B. Reacciones adversas a medicamentos: alergia a antibióticos, AINE, otros [Internet]. 2021 [cited 2023 Dec 9]. Available from: https://www.aeped.es/sites/default/files/documentos/21_ra_medicamentos_criterios-correg_21012020.pdf
58. Agencia Española del Medicamento y Productos Sanitarios. Informe sobre sospechas de reacciones adversas notificadas a medicamentos de uso humano o acontecimientos adversos ocurridos después de la vacunación [Internet]. 2023 [cited 2023 Dec 9]. Available from: https://www.aemps.gob.es/medicamentos-de-uso-humano/farmacovigilancia-de-medicamentos-de-uso-humano/informacion-de-sospechas-de-reacciones-adversas-a-medicamentos-de-uso-humano/informacion/
59. Strazzulla A, Postorino MC, Belfeki N, Iordache L, de Pontfarcy A, Pitsch A, et al. Risk of Multidrug Resistant Bacteria Acquisition in Patients with Declared β-Lactam Allergy during Hospitalization in Intensive Care Unit: A Retrospective Cohort Study (2007-2018). J Immunol Res. 2022;2022:8906316.
60. Saunders H, Shrestha R, Khadka S, Helgeson SA. Patient-reported penicillin allergy and intensive care unit outcomes in sepsis. J Allergy Clin Immunol Pract. 2023 Oct;
61. Agencia Española del Medicamento y Productos Sanitarios. Quinolonas y fluoroquinolonas de administración sistémica: nuevas restricciones de uso [Internet]. 2018 [cited 2023 Dec 9]. Available from: https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2018/docs/NI_MUH_FV-14-2018-quinolonas-fluoroquinolonas.pdf
62. Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. J Investig Allergol Clin Immunol. 2012;22(5):363–71.
63. Moreno E, Laffond E, Muñoz-Bellido F, Gracia MT, Macías E, Moreno A, et al. Performance in real life of the European Network on Drug Allergy algorithm in immediate reactions to beta-lactam antibiotics. Allergy. 2016 Dec;71(12):1787–90.
64. Iuliano S, Senn L, Moi L, Muller YD, Ribi C, Buss G, et al. Management of Beta-Lactam Antibiotics Allergy: A Real-Life Study. Front Allergy. 2022;3:853587.
65. Girard JP. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in men. Int Arch Allergy Appl Immunol. 1968;33(5):428–38.
66. Assem ES, Vickers MR. Tests for penicillin allergy in man. II. The immunological cross-reaction between penicillins and cephalospor-

ins. Immunology. 1974 Aug;27(2):255–69.

67. Suárez C, Gudiol F. Antibióticos betalactámicos. Enferm Infecc Microbiol Clin. 2009 Feb;27(2):116–29.
68. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. J Pediatr. 1998 Jan;132(1):137–43.
69. Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. Clin Exp Allergy. 2001 Mar;31(3):438–43.
70. Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. J Allergy Clin Immunol. 2010 Nov;126(5):994–9.
71. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med. 2004 Jul 6;141(1):16–22.
72. Frumin J, Gallagher JC. Allergic Cross-Sensitivity Between Penicillin, Carbapenem, and Monobactam Antibiotics: What are the Chances? Ann Pharmacother. 2009 Feb 3;43(2):304–15.
73. Terico AT, Gallagher JC. Beta-Lactam Hypersensitivity and Cross-Reactivity. J Pharm Pract. 2014 Dec 14;27(6):530–44.
74. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016 May 15;62(10):e51–77.
75. Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med. 2020 May 1;180(5):745–52.
76. Collins CD, Bookal RS, Malani AN, Leo HL, Shankar T, Scheidel C, et al. Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment. Open Forum Infect Dis. 2022 Jan 1;9(1).
77. Brockow K, Wurpts G, Trautmann A. Patients with questionable penicillin (beta-lactam) allergy: Causes and solutions. Allergol Select. 2022 Jan 1;6(01):33–41.
78. McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A, et al. Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae. N Engl J Med. 2019 Feb 21;380(8):791–3.
79. Barberán J, Mensa J, Fariñas C, Llinares P, Olaechea P, Palomar M, et al. [Recommendations of antimicrobial treatment in patients allergic to beta-lactam antibiotics]. Rev Esp Quimioter. 2008 Mar;21(1):60–82.
80. Lutgring JD, Balbuena R, Reese N, Gilbert SE, Ansari U, Bhatnagar A, et al. Antibiotic Susceptibility of NDM-Producing Enterobacterales Collected in the United States in 2017 and 2018. Antimicrob Agents Chemother. 2020 Aug 20;64(9).
81. SEMICYUC. Proyecto Neumonia Zero [Internet]. 2011 [cited 2024 Jan 11]. Available from: https://semicyuc.org/proyecto-neumonia-zero/
82. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095–128.
83. Rijkers GT, Pelton SI. The old man's friend. Pneumonia. 2018 Dec 25;10(1):8.
84. File TM, Ramirez JA. Community-Acquired Pneumonia. N Engl J Med. 2023 Aug 17;389(7):632–41.
85. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996 Jan 10;275(2):134–41.
86. Metersky ML, Waterer G, Nsa W, Bratzler DW. Predictors of In-Hospital vs Postdischarge Mortality in Pneumonia. Chest. 2012 Aug;142(2):476–81.
87. Walden AP, Clarke GM, McKechnie S, Hutton P, Gordon AC, Rello J, et al. Patients with community acquired pneumonia admitted to European intensive care units: an epidemiological survey of the GenOSept cohort. Crit Care. 2014 Apr 1;18(2):R58.
88. Cilloniz C, Ferrer M, Liapikou A, Garcia-Vidal C, Gabarrus A, Ceccato A, et al. Acute respiratory distress syndrome in mechanically ventilated patients with community-acquired pneumonia. Eur Resp J. 2018 Mar;51(3):1702215.
89. Kolditz M, Ewig S, Klapdor B, Schütte H, Winning J, Rupp J, et al. Community-acquired pneumonia as medical emergency: predictors of early deterioration. Thorax. 2015 Jun;70(6):551–8.
90. Kontou P, Kuti JL, Nicolau DP. Validation of the Infectious Diseases Society of America/American Thoracic Society criteria to predict severe community-acquired pneumonia caused by Streptococcus pneumoniae. Am J Emerg Med. 2009 Oct;27(8):968–74.
91. Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. Ann Am Thorac Soc. 2015 Feb;12(2):153–60.
92. Musher DM, Abers MS, Bartlett JG. Evolving Understanding of the Causes of Pneumonia in Adults, With Special Attention to the Role of Pneumococcus. Clin Infect Dis. 2017 Oct 30;65(10):1736–44.
93. Tleyjeh IM, Tlaygeh HM, Hejal R, Montori VM, Baddour LM. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. Clin Infect Dis. 2006 Mar 15;42(6):788–97.
94. Sader HS, Mendes RE, Le J, Denys G, Flamm RK, Jones RN. Antimicrobial Susceptibility of Streptococcus pneumoniae from North America, Europe, Latin America, and the Asia-Pacific Region: Results From 20 Years of the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis. 2019 Mar 15;6(Supplement_1):S14–23.
95. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis. 2007 Mar 1;44(Supplement_2):S27–72.

96. Martin-Loeches I, Torres A, Nagavci B, Aliberti S, Antonelli M, Bassetti M, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med. 2023 Jun 4;49(6):615–32.

97. Eljaaly K, Alshehri S, Aljabri A, Abraham I, Al Mohajer M, Kalil AC, et al. Clinical failure with and without empiric atypical bacteria coverage in hospitalized adults with community-acquired pneumonia: a systematic review and meta-analysis. BMC Infect Dis. 2017 Dec 2;17(1):385.

98. Wu M, Yang X, Tian J, Fan H, Zhang Y. Antibiotic Treatment of Pulmonary Infections: An Umbrella Review and Evidence Map. Front Pharmacol. 2021 Oct 19;12.

99. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589–96.

100. Scheeren TWL, Welte T, Saulay M, Engelhardt M, Santerre-Henriksen A, Hamed K. Early improvement in severely ill patients with pneumonia treated with ceftobiprole: a retrospective analysis of two major trials. BMC Infect Dis. 2019 Dec 26;19(1):195.

101. Eckburg PB, Friedland HD, Llorens L, Smith A, Witherell GW, Laudano JB, et al. Day 4 Clinical Response of Ceftaroline Fosamil Versus Ceftriaxone for Community-Acquired Bacterial Pneumonia. Infect Dis Clin Pract (Baltim Md). 2012 Jul;20(4):254–60.

102. Taboada M, Melnick D, Iaconis JP, Sun F, Zhong NS, File TM, et al. Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2016 Apr;71(4):862–70.

103. Cilloniz C, Mendez R, Peroni H, Garcia-Vidal C, Rico V, Gabarrus A, et al. Impact on in-hospital mortality of ceftaroline versus standard of care in community-acquired pneumonia: a propensity-matched analysis. Eur J Clin Microbiol Infect Dis. 2022 Feb 12;41(2):271–9.

104. Rodríguez AH, Avilés-Jurado FX, Díaz E, Schuetz P, Trefler SI, Solé-Violán J, et al. Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis. J Infect. 2016 Feb;72(2):143–51.

105. Dyar OJ, Huttner B, Schouten J, Pulcini C, ESGAP (ESCMID Study Group for Antimicrobial stewardshiP). What is antimicrobial stewardship? Clin Microbiol Infect. 2017 Nov;23(11):793–8.

106. Goff DA, Bauer KA, Reed EE, Stevenson KB, Taylor JJ, West JE. Is the 'low-hanging fruit' worth picking for antimicrobial stewardship programs? Clin Infect Dis. 2012 Aug;55(4):587–92.

107. Viasus D, Vecino-Moreno M, De La Hoz JM, Carratalà J. Antibiotic stewardship in community-acquired pneumonia. Expert Rev Anti Infect Ther. 2017 Apr;15(4):351–9.

108. Cyriac JM, James E. Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother. 2014 Apr;5(2):83–7.

109. AEMPS. Ficha técnica de cefditoren [Internet]. 2020 [cited 2023 Dec 22]. Available from: https://cima.aemps.es/cima/dochtml/ft/65975/FT_65975.html#5.2

110. Aliberti S, Zanaboni AM, Wiemken T, Nahas A, Uppatla S, Morlacchi LC, et al. Criteria for clinical stability in hospitalised patients with community-acquired pneumonia. Eur Respir J. 2013 Sep;42(3):742–9.

111. Kimura T, Ito M, Onozawa S. Switching from intravenous to oral antibiotics in hospitalized patients with community-acquired pneumonia: A real-world analysis 2010-2018. J Infect Chemother. 2020 Jul;26(7):706–14.

112. Athanassa Z, Makris G, Dimopoulos G, Falagas ME. Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. Drugs. 2008;68(17):2469–81.

113. Deshpande A, Klompas M, Guo N, Imrey PB, Pallotta AM, Higgins T, et al. Intravenous to Oral Antibiotic Switch Therapy Among Patients Hospitalized With Community-Acquired Pneumonia. Clin Infect Dis. 2023 Jul 26;77(2):174–85.

114. Engel MF, Postma DF, Hulscher MEJL, Teding van Berkhout F, Emmelot-Vonk MH, Sankatsing S, et al. Barriers to an early switch from intravenous to oral antibiotic therapy in hospitalised patients with CAP. Eur Respir J. 2013 Jan;41(1):123–30.

115. Menendez R, Montull B, Mendez R. Antibiotic choice, route and duration: minimising the harm associated with antibiotics. Eur Respir J. 2014 Mar;155–67.

116. Barberan J, Pueyo J. Cefditoren en las infecciones de vías respiratorias bajas adquiridas en la comunidad. Rev Esp Quimioter. 2009 Jan 1;22(3):144–50.

117. Sempere J, González-Camacho F, Domenech M, Llamosí M, Del Río I, López-Ruiz B, et al. A national longitudinal study evaluating the activity of cefditoren and other antibiotics against non-susceptible Streptococcus pneumoniae strains during the period 2004–20 in Spain. J Antimicrob Chemother. 2022 Mar 31;77(4):1045–51.

118. Cantón R, Barberán J, Linares M, Molero JM, Rodríguez-González-Moro JM, Salavert M, et al. Decalogue for the selection of oral antibiotics for lower respiratory tract infections. Rev Esp Quimioter. 2022 Jan 20;35(1):16–29.

119. Soriano Viladomiu A, Mensa Pueyo J, López Suñé E, Zboromyrska Y, Llinares Mondejar P, Barberán López J. Guía de Terapéutica antimicrobiana: 2023. 33rd ed. Barcelona: Antares; 2023.

120. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med. 2020 May 10;46(5):888–906.

121. Grupo de Trabajo de Enfermedades Infecciosas y Sepsis de la SEMICYUC (Sociedad Española de Medicina Intensiva Crítica y Unidades Coronarias). Estudio Nacional de Vigilancia de Infección Nosocomial en Servicios de Medicina Intensiva. Informe 2022. [Internet]. 2022 [cited 2023 Dec 15]. Available from: https://hws.vhebron.net/envin-helics/Help/Informe%20ENVIN-UCI%202022.pdf

122. Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2021 Feb;21(2):241–51.

123. Bonine NG, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, et al. Impact of Delayed Appropriate Antibiotic Therapy on Patient Outcomes by Antibiotic Resistance Status From Serious Gram-negative Bacterial Infections. Am J Med Sci. 2019 Feb;357(2):103–10.

124. Martin-Loeches I, Rodriguez AH, Torres A. New guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia: USA vs. Europe. Curr Opin Crit Care. 2018 Oct;24(5):347–52.

125. Mazzeffi M, Gammie J, Taylor B, Cardillo S, Haldane-Lutterodt N, Amoroso A, et al. Healthcare-Associated Infections in Cardiac Surgery Patients With Prolonged Intensive Care Unit Stay. Ann Thorac Surg. 2017 Apr;103(4):1165–70.

126. van Vught LA, Klein Klouwenberg PMC, Spitoni C, Scicluna BP, Wiewel MA, Horn J, et al. Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA. 2016 Apr 12;315(14):1469–79.

127. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med. 2019 Feb;45(2):172–89.

128. Detsis M, Karanika S, Mylonakis E. ICU Acquisition Rate, Risk Factors, and Clinical Significance of Digestive Tract Colonization With Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis. Crit Care Med. 2017 Apr;45(4):705–14.

129. Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012 Dec;38(12):1930–45.

130. Raman G, Avendano EE, Chan J, Merchant S, Puzniak L. Risk factors for hospitalized patients with resistant or multidrug-resistant Pseudomonas aeruginosa infections: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2018;7:79.

131. Zhu WM, Yuan Z, Zhou HY. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection relative to two types of control patients: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2020 Jan 31;9(1):23.

132. Brink AJ. Epidemiology of carbapenem-resistant Gram-negative infections globally. Curr Opin Infect Dis. 2019 Dec;32(6):609–16.

133. Brink AJ, Richards GA. The role of multidrug and extensive-drug resistant Gam-negative bacteria in skin and soft tissue infections. Curr Opin Infect Dis. 2020 Apr;33(2):93–100.

134. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017 Nov 13;65(11):1819–28.

135. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The Clinical Utility of Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications. Clin Infect Dis. 2018 Jun 18;67(1):1–7.

136. Hoang S, Georget A, Asselineau J, Venier AG, Leroyer C, Rogues AM, et al. Risk factors for colonization and infection by Pseudomonas aeruginosa in patients hospitalized in intensive care units in France. PLoS One. 2018;13(3):e0193300.

137. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care. 2020 Jan 30;24(1):29.

138. Garnacho-Montero J, Amaya-Villar R. The problem of multi-resistance in gram-negative bacilli in intensive care units: Treatment and prevention strategies. Med Intensiva. 2022 Jun;46(6):326–35.

139. Gracia-Ahufinger I, López-González L, Vasallo FJ, Galar A, Siller M, Pitart C, et al. The CARBA-MAP study: national mapping of carbapenemases in Spain (2014–2018). Front Microbiol. 2023 Sep 8;14.

140. Sastre-Femenia MÀ, Fernández-Muñoz A, Gomis-Font MA, Taltavull B, López-Causapé C, Arca-Suárez J, et al. Pseudomonas aeruginosa antibiotic susceptibility profiles, genomic epidemiology and resistance mechanisms: a nation-wide five-year time lapse analysis. Lancet Reg Health Eur. 2023 Nov;34:100736.

141. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance. Pharmacotherapy. 2019 Mar;39(3):261–70.

142. Burillo A, Marín M, Cercenado E, Ruiz-Carrascoso G, Pérez-Granda MJ, Oteo J, et al. Evaluation of the Xpert Carba-R (Cepheid) Assay Using Contrived Bronchial Specimens from Patients with Suspicion of Ventilator-Associated Pneumonia for the Detection of Prevalent Carbapenemases. PLoS One. 2016 Dec 16;11(12):e0168473.

143. Wheatley RM, Botelho J. Chasing resistance: analyzing the fight against hospital infections. Lancet Reg Health Eur. 2023 Nov;34:100740.

144. Pogue JM, Kaye KS, Veve MP, Patel TS, Gerlach AT, Davis SL, et al. Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2020 Jul 11;71(2):304–10.

145. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther. 2018 Dec;7(4):439–55.

146. Bassetti M, Giacobbe DR, Patel N, Tillotson G, Massey J. Efficacy and Safety of Meropenem-Vaborbactam Versus Best Available Therapy for the Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Patients Without Prior Antimicrobial Failure: A Post Hoc Analysis. Adv Ther. 2019 Jul;36(7):1771–7.

147. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018 Jan 6;66(2):163–71.

148. Castón JJ, Cano A, Pérez-Camacho I, Aguado JM, Carratalá J, Ramasco F, et al. Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study). J Antimicrob Chemother. 2022 Apr 27;77(5):1452–60.

149. Falcone M, Daikos GL, Tiseo G, Bassoulis D, Giordano C, Galfo V, et al. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase-Producing Enterobacterales. Clin Infect Dis. 2021 Jun 1;72(11):1871–8.

150. Kollef MH, Nováček M, Kivistik Ü, Réa-Neto Á, Shime N, Martin-Loeches I, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2019 Dec;19(12):1299–311.

151. Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. Clin Infect Dis. 2019 Nov 13;69(Suppl 7):S565–75.

152. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, et al. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. Drugs. 2019 Feb;79(3):271–89.

153. Mensa J, Barberán J, Soriano A, Llinares P, Marco F, Cantón R, et al. Antibiotic selection in the treatment of acute invasive infections by Pseudomonas aeruginosa: Guidelines by the Spanish Society of Chemotherapy. Rev Esp Quimioter. 2018 Feb;31(1):78–100.

154. Bouglé A, Tuffet S, Federici L, Leone M, Monsel A, Dessalle T, et al. Comparison of 8 versus 15 days of antibiotic therapy for Pseudomonas aeruginosa ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial. Intensive Care Med. 2022 Jul;48(7):841–9.

155. Dhanani JA, Diab S, Chaudhary J, Cohen J, Parker SL, Wallis SC, et al. Lung Pharmacokinetics of Tobramycin by Intravenous and Nebulized Dosing in a Mechanically Ventilated Healthy Ovine Model. Anesthesiology. 2019 Aug;131(2):344–55.

156. Goldstein I, Wallet F, Nicolas-Robin A, Ferrari F, Marquette CH, Rouby JJ. Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1375–81.

157. Ferrari F, Lu Q, Girardi C, Petitjean O, Marquette CH, Wallet F, et al. Nebulized ceftazidime in experimental pneumonia caused by partially resistant Pseudomonas aeruginosa. Intensive Care Med. 2009 Oct;35(10):1792–800.

158. Li Bassi G, Motos A, Fernandez-Barat L, Aguilera Xiol E, Chiurazzi C, Senussi T, et al. Nebulized Amikacin and Fosfomycin for Severe Pseudomonas aeruginosa Pneumonia: An Experimental Study. Crit Care Med. 2019 Jun;47(6):e470–7.

159. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. Respir Care. 2010 Jul;55(7):845–51.

160. Rello J, Solé-Lleonart C, Rouby JJ, Chastre J, Blot S, Poulakou G, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect. 2017 Sep;23(9):629–39.

161. Niederman MS, Alder J, Bassetti M, Boateng F, Cao B, Corkery K, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis. 2020 Mar;20(3):330–40.

162. Ehrmann S, Barbier F, Demiselle J, Quenot JP, Herbrecht JE, Roux D, et al. Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia. N Engl J Med. 2023 Nov 30;389(22):2052–62.

163. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. 2023;

164. AEMPS. Ficha técnica de Ceftazidima-Avibactam [Internet]. 2021 [cited 2024 Jan 11]. Available from: https://cima.aemps.es/cima/dochtml/ft/1161109001/FT_1161109001.html

165. Tsolaki V, Mantzarlis K, Mpakalis A, Malli E, Tsimpoukas F, Tsirogianni A, et al. Ceftazidime-Avibactam To Treat Life-Threatening Infections by Carbapenem-Resistant Pathogens in Critically Ill Mechanically Ventilated Patients. Antimicrob Agents Chemother. 2020;64(3).

166. Shields RK, Nguyen MH, Press EG, Chen L, Kreiswirth BN, Clancy CJ. Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in Klebsiella pneumoniae Carbapenemase-Producing K pneumoniae: A Case Report and Review of Literature. Open Forum Infect Dis. 2017;4(3).

167. AEMPS (Agencia Española del Medicamento y Productos Sanitarios). Ficha tecnica Meropenem-Vaborbactam AEMPS-CIMA [Internet]. 2023 [cited 2024 Feb 16]. Available from: https://cima.aemps.es/cima/dochtml/ft/1181334001/FT_1181334001.html

168. Sader HS, Huband MD, Castanheira M, Flamm RK. Pseudomonas aeruginosa Antimicrobial Susceptibility Results from Four Years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States. Antimicrob Agents Chemother. 2017;61(3).

169. Wang C, Yang D, Wang Y, Ni W. Cefiderocol for the Treatment of Multidrug-Resistant Gram-Negative Bacteria: A Systematic Review of Currently Available Evidence. Front Pharmacol. 2022;13.

170. Titov I, Wunderink RG, Roquilly A, Rodríguez Gonzalez D, David-Wang A, Boucher HW, et al. A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study). Clin Infect Dis. 2021 Dec 6;73(11):e4539–48.

171. AEMPS (Agencia Española del Medicamento y Productos Sanitarios). Informe de Posicionamiento Terapéutico de imipenem/cilastatina/relebactam (Recarbrio®) en el tratamiento de la neumonía adquirida en el hospital/neumonía asociada a ventilación mecánica con o sin bacteriemia y en el tratamiento de infecciones debidas a organismos aerobios Gram-negativos en adultos con opciones de tratamiento limitadas [Internet]. 2022 [cited 2024 Feb 16]. Available from: https://www.aemps.gob.es/informa/informes-de-posicionamiento-terapeutico/informe-de-posicionamiento-terapeutico-de-imipenem-cilastatina-relebactam-recarbrio-en-el-tratamiento-de-la-neumonia-adquirida-en-el-hospital-neumonia-asociada-a-ventilacion-mecanica-con-o-sin/

172. Langendonk RF, Neill DR, Fothergill JL. The Building Blocks of Antimicrobial Resistance in Pseudomonas aeruginosa: Implications for Current Resistance-Breaking Therapies. Front Cell Infect Microbiol. 2021;11.

173. Karakonstantis S, Kritsotakis EI, Gikas A. Treatment options for K. pneumoniae, P. aeruginosa and A. baumannii co-resistant to carbapenems, aminoglycosides, polymyxins and tigecycline: an approach based on the mechanisms of resistance to carbapenems. Infection. 2020;48(6):835–51.

174. Morroni G, Bressan R, Fioriti S, D'Achille G, Mingoia M, Cirioni O, et al. Antimicrobial Activity of Aztreonam in Combination with Old and New β-Lactamase Inhibitors against MBL and ESBL Co-Producing Gram-Negative Clinical Isolates: Possible Options for the Treatment of Complicated Infections. Antibiotics (Basel). 2021 Nov 3;10(11).

175. Canton R, Doi Y, Simner PJ. Treatment of carbapenem-resistant *Pseudomonas aeruginosa* infections: a case for cefiderocol. Expert Rev Anti Infect Ther. 2022;20(8):1077–94.

176. Savoldi A, Carrara E, Tacconelli E. Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list—authors' response. J Antimicrob Chemother. 2020;75(7):2018.

177. Shields RK, Paterson DL, Tamma PD. Navigating Available Treatment Options for Carbapenem-Resistant 'Acinetobacter baumannii-calcoaceticus' Complex Infections. Clin Infect Dis. 2023;76(Supplement_2):S179–93.

178. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022 Apr;28(4):521–47.

179. Flores-Treviño S, Bocanegra-Ibarias P, Camacho-Ortiz A, Morfín-Otero R, Salazar-Sesatty HA, Garza-González E. 'Stenotrophomonas maltophilia' biofilm: its role in infectious diseases. Expert Rev Anti Infect Ther. 2019;17(11):877–93.

180. Majumdar R, Karthikeyan H, Senthilnathan V, Sugumar S. Review on 'Stenotrophomonas maltophilia': An Emerging Multidrug- resistant Opportunistic Pathogen. Recent Pat Biotechnol. 2022;16(4):329–54.

181. Mojica MF, Ouellette CP, Leber A, Becknell MB, Ardura MI, Perez F, et al. Successful Treatment of Bloodstream Infection Due to Metallo-β-Lactamase-Producing Stenotrophomonas maltophilia in a Renal Transplant Patient. Antimicrob Agents Chemother. 2016 Sep;60(9):5130–4.

182. Pintado V, Ruiz-Garbajosa P, Aguilera-Alonso D, Baquero-Artigao F, Bou G, Cantón R, et al. Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria. Enferm Infecc Microbiol Clin. 2023;41(6):360–70.

183. Rodríguez A, Moreno G, Bodi M, Gomez J, Martín-Loeches I. Corticosteroids and RCTs against the supposed undervaluation of real data evidence. Crit Care. 2021 Aug 18;25(1):297.

184. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005 Feb 1;171(3):242–8.

185. Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med. 2022;48(8):1009–23.

186. Moreno G, Rodríguez A, Reyes LF, Gomez J, Sole-Violan J, Díaz E, et al. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. Intensive Care Med. 2018 Sep;44(9):1470–82.

187. Moreno G, Carbonell R, Martin-Loeches I, Solé-Violán J, Correig i Fraga E, Gómez J, et al. Corticosteroid treatment and mortality in mechanically ventilated COVID-19-associated acute respiratory distress syndrome (ARDS) patients: a multicentre cohort study. Ann Intensive Care. 2021;11(1):159.

188. Snijders D, Daniels JMA, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010 May 1;181(9):975–82.

189. Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. The Lancet. 2011 Jun;377(9782):2023–30.

190. Wittermans E, van der Zee PA, Qi H, van de Garde EMW, Blum CA, Christ-Crain M, et al. Community-acquired pneumonia subgroups and differential response to corticosteroids: a secondary analysis of controlled studies. ERJ Open Res. 2022 Jan;8(1):00489–2021.

191. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2017 Dec 13;12(12):CD007720.

192. Saleem N, Kulkarni A, Snow TAC, Ambler G, Singer M, Arulkumaran N. Effect of Corticosteroids on Mortality and Clinical Cure in Community-Acquired Pneumonia: A Systematic Review, Meta-analysis, and Meta-regression of Randomized Control Trials. Chest. 2023 Mar;163(3):484–97.

193. Wu JY, Tsai YW, Hsu WH, Liu TH, Huang PY, Chuang MH, et al. Efficacy and safety of adjunctive corticosteroids in the treatment of severe community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2023 Jul 8;27(1):274.

194. Chen S, Hu C. Effect of corticosteroids on mortality in patients with community-acquired pneumonia. Crit Care. 2023 Sep 19;27(1):358.

195. Chiang CH, See XY, Wang TH, Chang YC, Lo JE, Liu WT, et al. Effects of corticosteroids on severe community-acquired pneumonia: a closer look at the evidence. Crit Care. 2023 Aug 29;27(1):336.

196. Martin-Loeches I, Nagavci B, Torres A. Final approval for corticosteroids in severe CAP? For sure, in septic shock. Crit Care. 2023 Sep 4;27(1):342.

197. Luo M hao, Wan Z, Tu G wei, Luo Z. Comments on "Efficacy and safety of adjunctive corticosteroids in the treatment of severe community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials". Crit Care. 2023 Sep 6;27(1):348.

198. Pitre T, Rochwerg B, Zeraatkar D. Corticosteroids in Community-Acquired Pneumonia. Chest. 2023 Jan;163(1):e47–8.

199. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016 Aug;21(4):125–7.

200. World Health Organization (WHO). Sepsis [Internet]. 2023 [cited 2023 Dec 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/sepsis

201. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181–247.

202. Karavana V, Smith I, Kanellis G, Sigala I, Kinsella T, Zakynthinos S, et al. 37th International Symposium on Intensive Care and Emergency Medicine (part 1 of 3). Crit Care. 2017 Mar 21;21(S1):57.

203. Mesquida J, Borrat X, Lorente JA, Masip J, Baigorri F. Objetivos de la reanimación hemodinámica. Med Intensiva. 2011 Nov;35(8):499–508.

204. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus Low Blood-Pressure Target in Patients with Septic Shock. N Engl J Med. 2014 Apr 24;370(17):1583–93.

205. Adda I, Lai C, Teboul JL, Guerin L, Gavelli F, Monnet X. Norepinephrine potentiates the efficacy of volume expansion on mean systemic pressure in septic shock. Crit Care. 2021 Dec 21;25(1):302.

206. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. Crit Care. 2020 Aug 6;24(1):488.

207. Clark S, Barton G, Dean P, Mei Lau Y, Baldwin A. Guidance For: The use of Vasopressor Agents by Peripheral Intravenous Infusion in Adult Critical Care Patients [Internet]. 2023 [cited 2023 Dec 22]. Available from: https://ics.ac.uk/asset/3B607648%2D9292%2D4EC7%2DB913D5FCCA6F7D55/

208. Andaluz-Ojeda D, Cantón-Bulnes ML, Pey Richter C, Garnacho-Montero J. Fármacos vasoactivos en el tratamiento del shock séptico. Med Intensiva. 2022 May;46:26–37.

209. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015;10(8):e0129305.

210. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran S, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. N Engl J Med. 2016 Oct 27;375(17):1638–48.

211. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012 Oct;38(10):1573–82.

212. Gattinoni L, Marini JJ. Isn't it time to abandon ARDS? The COVID-19 lesson. Crit Care. 2021 Dec 6;25(1):326.

213. Domecq JP, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, et al. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. Crit Care Med. 2021 Mar 1;49(3):437–48.

214. Bos LDJ, Sjoding M, Sinha P, Bhavani S V, Lyons PG, Bewley AF, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. Lancet Respir Med. 2021 Dec;9(12):1377–86.

215. Maslove DM, Tang B, Shankar-Hari M, Lawler PR, Angus DC, Baillie JK, et al. Redefining critical illness. Nat Med. 2022 Jun 17;28(6):1141–8.

216. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023 Jul;49(7):727–59.

217. Ferguson ND, Frutos-Vivar F, Esteban A, Gordo F, Honrubia T, Peñuelas O, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. Crit Care. 2007;11(5):R96.

218. Grieco DL, Maggiore SM, Roca O, Spinelli E, Patel BK, Thille AW, et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive Care Med. 2021 Aug;47(8):851–66.

219. Goligher EC, Dres M, Patel BK, Sahetya SK, Beitler JR, Telias I, et al. Lung- and Diaphragm-Protective Ventilation. Am J Respir Crit Care Med. 2020 Oct 1;202(7):950–61.

220. Fernández-Mondéjar E, Fuset-Cabanes MP, Grau-Carmona T, López-Sánchez M, Peñuelas Ó, Pérez-Vela JL, et al. Empleo de ECMO en UCI. Recomendaciones de la Sociedad Española de Medicina Intensiva Crítica y Unidades Coronarias. Med Intensiva [Internet]. 2019 Mar [cited 2024 Jan 11];43(2):108–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0210569118302845

221. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351–63.

222. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018 May 24;378(21):1965–75.

223. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet. 2020 Oct 10;396(10257):1071–8.

224. Urner M, Barnett AG, Bassi GL, Brodie D, Dalton HJ, Ferguson ND, et al. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. BMJ. 2022 May 4;e068723.

225. Castaño M, Sbraga F, Pérez de la Sota E, Arribas JM, Cámara ML, Voces R, et al. Oxigenación con membrana extracorpórea en el paciente COVID-19: resultados del Registro Español ECMO-COVID de la Sociedad Española de Cirugía Cardiovascular y Endovascular. Cirugía Cardiovascular. 2022 Mar;29(2):89–102.

226. SEMICYUC. Informe ENVIN-UCI 2020-21 [Internet]. 2021 [cited 2024 Jan 11]. Available from: https://hws.vhebron.net/envin-helics/Help/Informe%20ENVIN-UCI%202021.pdf

227. Zangrillo A, Landoni G, Biondi-Zoccai G, Greco M, Greco T, Frati G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Crit Care Resusc. 2013 Sep;15(3):172–8.

228. Vaquer S, de Haro C, Peruga P, Oliva JC, Artigas A. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care. 2017 Dec;7(1):51.

229. Jamal JA, Economou CJP, Lipman J, Roberts JA. Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation. Curr Opin Crit Care. 2012 Oct;18(5):460–71.

230. Grasselli G, Scaravilli V, Di Bella S, Biffi S, Bombino M, Patroniti N, et al. Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome. Crit Care Med. 2017 Oct;45(10):1726–33.

231. Bouglé A, Bombled C, Margetis D, Lebreton G, Vidal C, Coroir M, et al. Ventilator-associated pneumonia in patients assisted by veno-arterial extracorporeal membrane oxygenation support: Epidemiology and risk factors of treatment failure. PLoS One. 2018 Apr 13;13(4):e0194976.

232. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med. 2003 Mar;31(3):676–82.

233. Hänsel L, Schumacher J, Denis B, Hamane S, Cornely OA, Koehler P. How to diagnose and treat a patient without human immunodeficiency virus infection having Pneumocystis jirovecii pneumonia? Clin Microbiol Infect. 2023 Aug 1;29(8):1015–23.

234. Zhou S, Aitken SL. Prophylaxis Against Pneumocystis jirovecii Pneumonia in Adults. JAMA. 2023 Jul 11;330(2):182–3.

235. Iriart X, Challan Belval T, Fillaux J, Esposito L, Lavergne RA, Cardeau-Desangles I, et al. Risk factors of Pneumocystis pneumonia in solid organ recipients in the era of the common use of posttransplantation prophylaxis. Am J Transplant. 2015 Jan;15(1):190–9.

236. Viceconte G, Buonomo AR, D'Agostino A, Foggia M, Di Fusco A, Pinchera B, et al. Risk Factors for Pneumocystis jirovecii Pneumonia in Non-HIV Patients Hospitalized for COVID-19: A Case-Control Study. J Fungi (Basel). 2023 Aug 11;9(8).

237. Amstutz P, Bahr NC, Snyder K, Shoemaker DM. 'Pneumocystis jirovecii' Infections Among COVID-19 Patients: A Case Series and Literature Review. Open Forum Infect Dis. 2023 Feb 3;10(2).

238. Goterris L, Mancebo Fernández MA, Aguilar-Company J, Falcó V, Ruiz-Camps I, Martín-Gómez MT. Molecular Diagnosis of Pneumocystis jirovecii Pneumonia by Use of Oral Wash Samples in Immunocompromised Patients: Usefulness and Importance of the DNA Target. J Clin Microbiol. 2019 Dec;57(12).

239. Lieu A, Lee TC, Lawandi A, Tellier R, Cheng MP, Dufresne PJ. Microbiological characterization of 'Pneumocystis jirovecii' pneumonia using quantitative PCR from nasopharyngeal specimens: a retrospective study in a Canadian province from 2019 to 2023. J Clin Microbiol. 2023 Nov 21;61(11).

240. Veintimilla C, Álvarez-Uría A, Martín-Rabadán P, Valerio M, Machado M, Padilla B, et al. Pneumocystis jirovecii Pneumonia Diagnostic Approach: Real-Life Experience in a Tertiary Centre. J Fungi (Basel). 2023 Mar 28;9(4):414.

241. Morjaria S, Frame J, Franco-Garcia A, Geyer A, Kamboj M, Babady NE. Clinical Performance of (1,3) Beta-D Glucan for the Diagnosis of Pneumocystis Pneumonia (PCP) in Cancer Patients Tested With PCP Polymerase Chain Reaction. Clin Infect Dis. 2019 Sep 27;69(8):1303–9.

242. Friedrich R, Rappold E, Bogdan C, Held J. Comparative Analysis of the Wako β-Glucan Test and the Fungitell Assay for Diagnosis of Candidemia and Pneumocystis jirovecii Pneumonia. J Clin Microbiol. 2018 Sep;56(9).

243. Apostolopoulou A, Fishman JA. The Pathogenesis and Diagnosis of Pneumocystis jiroveci Pneumonia. J Fungi (Basel). 2022 Nov 5;8(11).

244. Del Corpo O, Butler-Laporte G, Sheppard DC, Cheng MP, McDonald EG, Lee TC. Diagnostic accuracy of serum (1-3)-β-D-glucan for Pneumocystis jirovecii pneumonia: a systematic review and meta-analysis. Clin Microbiol Infect. 2020 Sep;26(9):1137–43.

245. Bigot J, Vellaissamy S, Senghor Y, Hennequin C, Guitard J. Usefulness of ß-d-Glucan Assay for the First-Line Diagnosis of Pneumocystis Pneumonia and for Discriminating between Pneumocystis Colonization and Pneumocystis Pneumonia. J Fungi (Basel). 2022 Jun 24;8(7):663.

246. Burzio C, Balzani E, Corcione S, Montrucchio G, Trompeo AC, Brazzi L. Pneumocystis jirovecii Pneumonia after Heart Transplantation: Two Case Reports and a Review of the Literature. Pathogens. 2023 Oct 21;12(10):1265.

247. Lagrou K, Chen S, Masur H, Viscoli C, Decker CF, Pagano L, et al. Pneumocystis jirovecii Disease: Basis for the Revised EORTC/MSGERC Invasive Fungal Disease Definitions in Individuals Without Human Immunodeficiency Virus. Clin Infect Dis. 2021 Mar 12;72(Suppl 2):S114–20.

248. Moreno A, Epstein D, Budvytiene I, Banaei N. Accuracy of Pneumocystis jirovecii Plasma Cell-Free DNA PCR for Noninvasive Diagnosis of Pneumocystis Pneumonia. J Clin Microbiol. 2022 May 18;60(5):e0010122.

249. Li X, Xiong X, Liang Z, Tang Y. A machine learning diagnostic model for Pneumocystis jirovecii pneumonia in patients with severe pneumonia. Intern Emerg Med. 2023 Sep;18(6):1741–9.

250. Sohani ZN, Butler-Laporte G, Aw A, Belga S, Benedetti A, Carignan A, et al. Low-dose trimethoprim-sulfamethoxazole for the treatment of Pneumocystis jirovecii pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial. BMJ Open. 2022 Jul 21;12(7):e053039.

251. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax. 2015;70(3):270–7.

252. Nucci M, Nouer SA, Cappone D, Anaissie E. Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome. Haematologica. 2013;98(11):1657–60.

253. Koulenti D, Papathanakos G, Blot S. Invasive pulmonary aspergillosis in the ICU: tale of a broadening risk profile. Curr Opin Crit Care.

2023;29(5):463–9.

254. Peral J, Estella Á, Nuvials X, Rodríguez A, Seijas I, Soriano C, et al. Managing the Next Wave of Influenza and/or SARS-CoV-2 in the ICU—Practical Recommendations from an Expert Group for CAPA/IAPA Patients. J Fungi (Basel). 2023;9(3):312.

255. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R, et al. The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin. Drugs. 2021 Oct;81(15):1703–29.

256. Douglas AP, Smibert OC, Bajel A, Halliday CL, Lavee O, McMullan B, et al. Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021. Intern Med J. 2021 Nov;51 Suppl 7:143–76.

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Raúl Ortíz de Lejarazu[1]
José M. Eiros[2]
Francisco López-Medrano[3]
Milagros Montes[4]
Alfredo Tagarro[5]
María Tomás[6]

The role of viral diagnostic tests in respiratory tract infections: moving forward

[1]Scientific Advisory y Director Emérito del Centro Nacional de Gripe. Hospital Clínico de Valladolid
[2]Centro Nacional de Gripe de Valladolid.
[3]Hospital Universitario 12 de Octubre.
[4]Hospital Universitario de Donostia.
[5]Instituto de Investigación 12 de Octubre; Hospital Infanta Sofía
[6]Hospital Universitario de a Coruña.

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ABSTRACT

The increased knowledge on virology and the increased potential of their diagnostic has risen several relevant question about the role of an early viral diagnosis and potential early treatment on the management of respiratory tract infections (RTI). In order to further understand the role of viral diagnostic tests in the management of RTI, a panel of experts was convened to discuss about their potential role, beyond what had been agreed in Influenza. The objective of this panel was to define the plausible role of aetiologic viral diagnostic into clinical management; make recommendations on the potential expanded use of such tests in the future and define some gaps in the management of RTI. Molecular Infection Viral Diagnostic (mIVD) tests should be used in all adult patients admitted to Hospital with RTI, and in paediatric patients requiring admission or who would be referred to another hospital for more specialised care. The increased use of mIVD will not only reduce the inappropriate use of antibiotics so reducing the antibiotic microbe resistance, but also will improve the outcome of the patient if an aetiologic viral therapy can be warranted, saving resource requirements and improving patient flows. Implementing IVD testing in RTI has various organizational benefits as well, but expanding its use into clinical settings would need a cost-effectiveness strategy and budget impact assessment.

Keywords: respiratory tract infection, viral diagnostic tests, molecular diagnostic tests

Correspondence:
Dr. Raúl Ortíz de Lejarazu
Scientific Advisory y Director Emérito del Centro Nacional de Gripe. Hospital Clínico de Valladolid
E-mail: lejarazu@gmail.com

El papel de las pruebas de diagnóstico virológico en las infecciones de las vías respiratorias: Hay que avanzar

RESUMEN

El aumento del conocimiento virológico y el mayor potencial de su diagnóstico ha planteado una serie de preguntas relevantes sobre el papel de un diagnóstico viral precoz y así la posibilidad de un tratamiento precoz dirigido para el manejo de las infecciones del tracto respiratorio (ITR). Con el fin de comprender mejor el papel de las pruebas diagnósticas virales en el manejo de la ITR, se convocó a un panel de expertos para discutir sobre el posible uso de dicho diagnóstico vírico, más allá de lo establecido en documentos previos acordados para la gripe. El objetivo del panel fue comprender la plausibilidad del diagnóstico viral etiológico precoz en el manejo clínico; formular algunas recomendaciones sobre la posible ampliación del uso de dichas pruebas en el futuro y definir algunas lagunas en la gestión sanitaria de la ITR.

Las pruebas de diagnóstico viral de infección molecular (mIVD) deben utilizarse en todos los pacientes adultos ingresados en el hospital con ITR, y en determinados pacientes pediátricos que requieran ingreso o que sean derivados a otro hospital para recibir atención más especializada. El aumento del uso de mIVD no solo reducirá el uso inadecuado de antibióticos, reduciendo así la resistencia microbiana a los antibióticos, sino que también mejorará el resultado del paciente si se inicia una terapia viral etiológica, reduciendo consumo de recursos y mejorando los flujos de pacientes. Asimismo, existen beneficios organizativos en la implementación de pruebas de diagnóstico in vitro en la ITR que requerirán una estimación del impacto presupuestario y un enfoque de rentabilidad para una mayor penetración en su uso clínico.

Palabras clave: infecciones del tracto respiratorio, pruebas de diagnóstico viral, pruebas de diagnóstico molecular

INTRODUCTION

In February 2023 a consensus on the management of Influenza was published [1]. After the COVID pandemic this helped to raise the awareness on the potential benefits of an accurate management of viral infections [2]. This followed NICE's guideline for the treatment and prevention of neonatal infections, guidelines on the usage of diagnostic tests in emergency care [3] or an evaluation by NIHR on the benefits of early testing and rapid isolation [4]. The increased knowledge on virology and the increased potential of virus diagnostic has risen a series of relevant question on the role of an early diagnostic and potential early treatment on the management of respiratory tract infections (RTI). As with other diseases, the advent of a diagnostic technology paired with targeted therapies has raised questions regarding the pathogenic role of these infections as well as the need to better understand the impact of their use on the management of healthcare burden.

To further understand the role of viral diagnostic tests in the management of RTI, a panel of experts were convened to discuss about their potential role, beyond what had been agreed in Influenza. The objective of this panel was to advise on the plausible role of aetiologic viral diagnostic into clinical management, making some recommendations on the potential expanded use of such tests in the future and to define some gaps in the management of RTI.

METHODS

Six leading Spanish physicians (1 Paediatrician, 1 Infectologist, and 4 Microbiologists from 5 leading Spanish Hospitals) were convened in July 2023 at a round discussion on the definition of the needs and benefits of an aetiologic infection viral diagnostic (IVD) approach and the profiling of the target population of that IVD approach.

The meeting was an unblinded open discussion following a pre-defined semi-structured questionnaire (Supplementary material – Annex 1), facilitated by a third party. Each section of the text corresponds to the discussion around each of the 3 main discussed topics. Despite the meeting was commissioned by a manufacturing company, they did not participate in the meeting, nor directly nor as external listeners.

In terms of evidence grading, the purpose of the meeting was not to construct a Clinical Practice Guideline, but rather a more modest aim of pointing out new avenues to pursue next.

RESULTS

Why do we need aetiologic RTI IVD?. In the current context of upper and lower RTI it is well know that there is a significant number of respiratory syndromes where a coinfection (bacterial and viral) exists. The absence of an accurate viral diagnostic leads to an aetiologic diagnostic for bacterial only, leaving the viral fraction unexplored and unexplained. However, there is increasing evidence on the relevance of viral coinfection in the prognosis of the episodes of RTI [5,6], linking viruses to potential increasing severity of bacterial infections. This includes the detection of SARS-CoV-2 [7] as a relevant prognostic factor [8,9]. Viral infection also constitutes a risk for other clinical events such as acute myocardial infarction, stroke, etc. Several hypotheses have been generated, among them, the downstream dysregulation of the inflammatory cascade could be a prominent factor [10,11]. Therefore, the lack of an accurate diagnostic procedure, where viruses can be precisely diagnosed is not only underperforming care, but could also result in a harm to patients that may be put at risk of unsuspected more severe diseases and/or further complications.

The concept of "*Driver*" versus "*Passenger*" virus needs to be further defined, and the importance and role of each bacterial or viral pathogen on RTI must be clearly elucidated. Understanding whether clinician is facing a bacterial or viral infection is key for future treatment options, and therefore there is a need to clearly identify the viral pathogens in the sample and then to apply clinical judgement to decide whether is it a driver or a passenger virus. In this way, the interaction between the clinician and the microbiologist may shed light into the role of each pathogen in the RTI clinical presentation. The absence of acceptable biomarkers in this field will require the participation of both specialist in the management of the patient and the selection of the appropriate treatment(s). Ruling out the involvement of the '*Big Five*' (namely, Influenza A&B, RSV, SARS-CoV-2, Rhinovirus, and Adenovirus) will certainly be a first step towards an accurate and targeted therapeutic strategy.

An important factor limiting the access and implementation of IVD in RTI is the limited understanding of the potential benefits of that technology. One of the obvious reasons why viral testing is required is the need to incorporate the viral information in the therapeutic decision process, and therefore on the decision for an antibiotic treatment. This has implications for antimicrobial resistance (AMR) policies and important societal consequences of those policies. Within the framework of the PROA project [12], one justification for the existence of specific viral diagnostic tools is the appropriate use of antibiotics.

Beyond this, is important to know if the patient will benefit from an antibiotic or is it just a risk or a potential source of adverse side effects? An appropriately diagnosed patient could benefit, when available, from targeted antiviral therapy, meaning the patient's potential outcome would improve. Limiting the arsenal of treatments to "what we know" is limiting the progress and efficiency of our healthcare systems. Especially now that an increasing number of the "Big Five" have specific viral therapies that could relieve pressure on health services and improve patient outcomes. It might be appropriate to also include parainfluenza virus, metapneumovirus or bocavirus. Furthermore, given that the incidence of SARS-CoV-2 is decreasing as other viruses regain their space, the preponderance of the remaining therapies is worth highlighting.

Taking into account the need to apply targeted viral therapies, there is a need to make an adequate and timely etiological diagnosis. Along with the known benefits of an early start of treatment, taking the necessary measures as soon as possible, combining them with known therapeutic agents is the most appropriate way for an efficient result. This includes the implementation of isolation policies, contact tracing and surveillance when necessary, reducing the need for complementary tests, preventing complications and, no less important, designing bed management policies with the aim of optimizing resources at the hospital level.

However, an adequate analysis of the economic impact of all these benefits has not been carried out yet. Administration, policymakers, and access managers would benefit from such information, as well as a sound economic evaluation.

There are several epidemic aspects that need to be known, as they may affect the management of paediatric and adult/elderly population with a different seasonal post-pandemic pattern than we used to know. After COVID19 pandemic the seasonal pattern of some respiratory pathogens have been lost, or at least have been severely disrupted and not recovered yet. This might have consequences at the level of suspected pathogenic agents when patients presenting with RTI at a certain sesonal time of the year. The knowledge of this changing epidemiology could have an impact on the planning requirements at the level of hospital admissions, emergency care wards and general practitioners (GP).

There is also a need to inform non-specialized medical providers about the relevance of viral etiological diagnosis, in terms of its potential benefits, when and who should perform it, since some of the health providers may not be fully aware of these issues. It is also not adequately known how viral load is not a binary biomarker (present or absent, positive or negative), but rather an important additional viral information that must be co-interpreted with the clinician at different times in the management of the patient, especially if the patient presents an unfavourable evolution

An important question is whether the aetiologic viral diagnostic should be available in both for GP and the Hospital setting, as both can benefit although in different ways. The IVD at the hospital should be available 24hours/7days, and if possible, it should be extended to the home setting. The home setting would be mostly appropriate when the 'deferred treatment onset' is considered, since visits to the clinic facilities could be reduced so decreasing the potential for further spread of infection. This broader access to IVD should be combined with a broader information from the sentinel networks, that should be made more readily available so that prescribing physicians can interpret the results more accurately. The epidemic information provided by surveillance networks and sentinels observatories should be maintained and reinforced after pandemic.

Widespread access to such information raises concerns about the readiness of information systems (and the ability of users to obtain such information), thus being able to timely incorporate and disseminate rapidly changing knowledge. This is necessary throughout the healthcare system, especially in certain clinical facilities, where the result may be available quickly but not accessible to doctors due to administrative constraints. A more "democratic" approach will be necessary for this information network, possibly integrating tools that are not available yet (mobile apps, portable devices, etc).

To achieve that goal and all their benefits be accessible, the tests must be affordable, possibly with a lower price for IVD tests used at the point of care. For many healthcare facilities, the budget impact of widespread use of IVD technologies will be of great concern, especially if the benefits of such early diagnosis are not well explained. Furthermore, an acceptable and methodologically sound economic evaluation of IVD testing in RTI is required for different healthcare settings.

What Tests? Although the group convened around the need of making the tests accessible and almost universal (home, GP and Hospital settings), they acknowledged there is a lack of consensus about which is the appropriate test in every setting.

Hospitals may use molecular IVD (mIVD) testing (based on PCR testing) as it has been shown to be effective and affordable. In adults its use is not discussed. In paediatric patients, although more evidence may be needed and there are budgetary implications, having an IVD test with the same sensitivity and specificity as in adults could lead to its universal use.

In outpatient settings, mDIV would ideally be used as it has been shown to be more reliable (better negative predictive performance). However, given the cost and high number of tests in those primary healthcare facilities, they may not be appropriate in the outpatient setting for all RTI patients, and the expert proposal should be to use non-molecular IVD (nmIVD) testing (ie. antigen-based testing) in outpatient settings. If reduced trial pricing policies could be implemented, then a different access strategy could be pursued. This does not mean that mIVDs should not be available in the outpatient setting, but rather that their use may be limited to some particular cases due to budgetary pressure. Alternatively, nmIVD could be used in epidemic periods, while there is high virus circulation within the community, accepting that its more limited accuracy is balanced by the lower severity of cases. Otherwise, the case would be sent to the hospital where mIVD would be

Table 1 Suggested tests in healthcare diagnostic settings

	Hospital Setting		Ambulatory Care	
	Adults	Paediatric	Adults	Paediatric
nmIVD	-	-	++	++
mIVD	+++	+++	+	+

nmIVD: non-molecular infection viral diagnostic

mIVD: molecular infection viral diagnostic

performed (Table 1).

Whatever the test, the result of an mIVD should be available in less than or equal to 30 minutes; Any delay beyond that could potentially lead to dysfunctions in clinical management. In an outpatient setting, especially in paediatrics, test turnaround time (excluding management time) should be less than 10 minutes as there is a risk of overwhelming outpatient settings. Tests based on nmIVD have a lower negative predictive value, the result is influenced by the epidemic predominant virus and should not be administered to any person with less than 48 hours of evolution, although accepting it could have a negative impact on treatment.

CRISPR technologies [13] (gene editing techniques) should be looked at also as a potential future alternative, understanding their potential and the appropriate positioning amongst patients. For any future alternative to be established and acceptable a minimum performance should be required. The minimum would be set at >96% sensitivity and > 98% positive predictive value. This may be challenging, given that regulatory agencies (i.e. ECDC [14]) require only 80% [15]. Stratification of patients' risk should be needed, to reduce the number needed to test.

Any test should cover >50% potential aetiological pathogens to be fully implemented and will only be credible if it has >2 virus targets. This information needs to be contrasted and updated along the epidemiologic information.

For whom? The discussion about to what patients the mIVD should be used can be seen in two different situations: without knowing and knowing the cost. Regarding the former, the group agreed that all RTI patients would be candidates for mIVD, although a stricter criterion would be to use them in outpatient care when a patient is going to be referred to the hospital for further diagnosis or treatment. In this context, clinical judgment must prevail and be the guiding principle; The intensity of symptoms should trigger medical actions, not diagnostic tests. In the hospital setting, regardless of price, all severe RTI patients and those admitted with RTI should have mIVD testing.

In primary care, priority should be given to antigen tests, despite their lower performance capacity, considered too low and unacceptable for many professionals. However, in the hospital setting, at the current cost, all admitted patients should have mIVD testing, especially those on oxygen therapy either in or out of the ICU, the immunocompromised, and those with underlying comorbidities. There was agreement that patients with RTI to be IVD tested should be the same as those considered in the Influenza Consensus document [1]. Similarly, critically ill and immunocompromised patients in the Emergency Unit should have an mIVD test upon arrival.

In the paediatric ambulatory population, there were less consensus on which is the most appropriate attitude. According to the cost, the budget impact may not be affordable, but both at the hospital and the ambulatory setting, an mIVD may be very effective in those children that may be need transferred to a different hospital, or where a targeted therapy may be initiated.

NmIVD and mIVD diagnostic testing should be performed as a priority in those patients in whom knowledge of the precise diagnosis provides additional value and/or targeted therapy can be initiated immediately. Otherwise, it may be perceived as a waste of resources. Patients with RTI without risk factors or serious symptoms should not be tested and non-pharmacological measures should be recommended (masks, social distancing, etc.).

CONCLUSIONS

The meeting highlighted and agreed on the potential use of mIVD in all adult RTI patients admitted to hospital and in some paediatric patients who require admission or who would be referred to another hospital for more specialized care. Increased use of mIVD will not only reduce inappropriate antibiotic use (reducing AMRs), but will also improve patient outcome if targeted viral therapy is initiated, thus reducing resource needs and improving patient flows. Additionally, there are several operational benefits to implementing IVD testing in RTI patients. Many of them will require a budget impact estimate and cost-effectiveness approach before broader implementation.

Because viral treatments must be started early to be as effective as possible, rapid diagnosis (ideally by 30 minutes) at an appropriate cost is needed. NmIVDs are not sufficient for hospitalized patients given their low negative predictive value, but they could be an affordable option in primary care for early management of positive cases.

Effort should be made to better characterize and quantify the benefits of this otherwise well-recognized need to "Treat early to benefit sooner".

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. López-Medrano F, Alfayate S, Carratalà J, Chamorro-Camazón J, Cordero E, Cruz-Cañete M, et al. Executive summary. Diagnosis, treatment and prophylaxis of influenza virus infection. Enferm Infecc Microbiol Clin 2023;41(2):111-22. DOI: 10.1016/j.eimc.2022.10.010
2. Overview | Neonatal infection: antibiotics for prevention and treatment | Guidance | NICE [Internet]. NICE; 2021 [cited 16/03/2024]. Available at: https://www.nice.org.uk/guidance/ng195
3. Stamm BD, Tamerius J, Reddy S, Barlow S, Hamer C, Kempken A, et al. The Influence of Rapid Influenza Diagnostic Testing on Cli-

nician Decision-Making for Patients With Acute Respiratory Infection in Urgent Care. Clin Infect Dis Off Publ Infect Dis Soc Am. 2023;76(11):1942-8. DOI: 10.1093/cid/ciad038

4. Rapid tests for flu reduce spread of disease in hospital - NIHR Evidence. [cited 16/03/2024]. Disponible en: https://evidence.nihr.ac.uk/alert/rapid-tests-flu-meant-earlier-treatment-isolation-less-serious-illness/
5. Jung J, Seo E, Yoo RN, Sung H, Lee J. Clinical significance of viral–bacterial codetection among young children with respiratory tract infections. Medicine (Baltimore) 2020;99(2):e18504. DOI: 10.1097/MD.0000000000018504
6. Hendaus MA, Jomha FA, Alhammadi AH. Virus-induced secondary bacterial infection: a concise review. Ther Clin Risk Manag. 2015;11:1265-71. DOI: 10.2147/TCRM.S87789
7. Yang MC, Su YT, Chen PH, Tsai CC, Lin TI, Wu JR. Changing patterns of infectious diseases in children during the COVID-19 pandemic. Front Cell Infect Microbiol. 2023;13:1200617. DOI: 10.3389/fcimb.2023.1200617
8. Ortega H, Nickle D, Carter L. Rhinovirus and asthma: Challenges and opportunities. Rev Med Virol 2021;31(4):e2193. DOI: 10.1002/rmv.2193
9. Sanz I, Rojo S, Eiros JM, Tamames S, Vega T, Ortiz de Lejarazu R. Simultaneous influenza Aand B infection in a pregnant woman in the context of influenza A family cluster. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2015;73:52-4. DOI: 10.1016/j.jcv.2015.10.017
10. Paquette SG, Banner D, Zhao Z, Fang Y, Huang SSH, León AJ, et al. Interleukin-6 is a potential biomarker for severe pandemic H1N1 influenza A infection. PloS One.2012;7(6):e38214. DOI: 10.1371/journal.pone.0038214
11. Villeret B, Solhonne B, Straube M, Lemaire F, Cazes A, Garcia-Verdugo I, et al. Influenza A Virus Pre-Infection Exacerbates Pseudomonas aeruginosa-Mediated Lung Damage Through Increased MMP-9 Expression, Decreased Elafin Production and Tissue Resilience. Front Immunol. 2020;11:117. DOI: 10.3389/fimmu.2020.00117
12. Programas de Optimización de Uso de los Antibióticos (PROA). [cited 17/11/2023]. Available at: https://www.resistenciaantibioticos.es/es/lineas-de-accion/control/programas-de-optimizacion-de-uso-de-los-antibioticos-proa
13. Rajan A, Shrivastava S, Janhawi null, Kumar A, Singh AK, Arora PK. CRISPR-Cas system:from diagnostic tool to potential antiviral treatment. Appl Microbiol Biotechnol. 2022;106(18):5863-77. DOI: 10.1007/s00253-022-12135-2
14. ECDC. Options for the use of rapid antigen tests for COVID-19 in the EU/EEA - first update. 2021 [cited 16/03/2024]. Available at: https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-first-update
15. WHO. Antigen-detection in the diagnosis of SARS-CoV-2 infection [Internet]. [cited 16/03/2024]. Available at: https://www.who.int/publications-detail-redirect/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

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Utilidad del modelo MPB-INFURG-SEMES para predecir bacteriemia en el paciente con neoplasia sólida en el Servicio de Urgencias

María Muelas González[1]
Elena Torner Marchesi[1]
Gabriela Peláez Díaz[1]
Marta Ramos Aranguez[1]
Javier Cabañas Morafraile[2]
William López Forero[2]
Rafael Rubio Díaz[2]
Juan González del Castillo[3]
Francisco Javier Candel[4]
Agustín Julián-Jiménez[2,5]
en nombre del grupo INFURG-SEMES (Adenda).

[1]Servicio de Oncología Médica, Complejo Hospitalario Universitario de Toledo, IDISCAM, Toledo, España.
[2]Servicio de Urgencias, Complejo Hospitalario Universitario de Toledo, IDISCAM, Toledo, España.
[3]Servicio de Urgencias, Hospital Universitario Clínico San Carlos, IDISSC, Madrid, España.
[4]Servicio de Microbiología Clínica, Hospital Universitario Clínico San Carlos, IDISSC, Madrid, España.
[5]Universidad de Castilla La Mancha.

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RESUMEN

Objetivo. Analizar la utilidad de un nuevo modelo predictivo de bacteriemia (MPB-INFURG-SEMES) en pacientes con neoplasia sólida atendidos por infección en el servicio de urgencias (SU).

Pacientes y métodos. Estudio observacional de cohortes prospectivo y multicéntrico de los hemocultivos (HC) obtenidos de pacientes adultos con neoplasia sólida atendidos en 63 SU por infección desde el 1 de noviembre de 2019 hasta el 31 de marzo de 2020. Se analizó la capacidad predictiva del modelo con el área bajo la curva (ABC) de la característica operativa del receptor (COR) y se calculó el rendimiento diagnóstico del punto de corte (PC) del modelo elegido con los cálculos de la sensibilidad, la especificidad, el valor predictivo positivo y el valor predictivo negativo.

Resultados. Se incluyeron 857 episodios de HC extraídos. De ellos, se consideraron como bacteriemias verdaderas 196 (22,9%) y como HC negativos 661 (77,1%). Entre los negativos, 42 (4,9%) se consideraron contaminados. El ABC-COR del modelo aplicado fue de 0,923 (IC 95%: 0,896-0,950). El rendimiento diagnóstico del modelo con un PC ≥ 5 puntos consigue una sensibilidad de 95,74% (IC 95%: 94,92-96,56), especificidad de 76,06% (IC 95%: 75,24-76,88) un valor predictivo positivo de 53,42% (IC 95%: 52,60-54,24) y un valor predictivo negativo de 98,48% (IC 95%: 97,66-99,30).

Conclusión. El modelo MPB-INFURG-SEMES podría ser útil para predecir bacteriemia en los pacientes adultos con neoplasia sólida atendidos en el SU por un episodio de infección.

Palabras clave: Tumor sólido. Bacteriemia. Modelo predictivo. Hemocultivos. Procalcitonina. Escala pronóstica. Servicio de Urgencias.

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. España.
E-mail: agustinj@sescam.jccm.es

Usefulness of the MPB-INFURG-SEMES model to predict bacteremia in the patient with solid tumor in the Emergency Department

ABSTRACT

Objective. To analyse a new risk score to predict bacteremia (MPB-INFURG-SEMES) in the patients with solid tumor attender for infection in the emergency departments (ED).

Patients and methods. Prospective, multicenter observational cohort study of blood cultures (BC) obtained from adult patients with solid neoplasia treated in 63 EDs for infection from November 1, 2019, to March 31, 2020. The predictive ability of the model was analyzed with the area under the Receiver Operating Characteristic curve (AUC-ROC). The prognostic performance for true bacteremia was calculated with the chosen cut-off for getting the sensitivity, specificity, positive predictive value and negative predictive value.

Results. A total of 857 blood samples wered cultured. True cases of bacteremia were confirmed in 196 (22.9%). The remaining 661 cultures (77.1%) wered negative. And, 42 (4.9%) were judged to be contaminated. The model's area under the receiver operating characteristic curve was 0.923 (95% CI, 0.896-0.950). The prognostic performance with a model's cut-off value of ≥ 5 points achieved 95.74% (95% CI, 94,92-96.56) sensitivity, 76.06% (95% CI, 75.24-76.88) specificity, 53.42% (95% CI, 52.60-54.24) positive predictive value and 98.48% (95% CI, 97.66- 99.30) negative predictive value.

Conclusion. The MPB-INFURG-SEMES score is useful for predicting bacteremia in the adults patients with solid tumor seen in the ED.

Keywords: Solid tumor. Bacteraemia. Clinical prediction rule. Blood cultures. Procalcitonin. Risk score. Emergency Department.

INTRODUCCIÓN

En la actualidad, la atención de pacientes con sospecha de un proceso infeccioso en los servicios de urgencias hospitalarios (SUH) se ha incrementado significativamente en las últimas décadas y supone, al menos, el 15% de todas las atenciones diarias (hasta el 40-50% en los picos de epidemias víricas) [1,2]. Además, la gravedad de su presentación clínica, la existencia de bacteriemia y la mortalidad intrahospitalaria y a corto plazo (30 días) también han aumentado, especialmente en aquellos pacientes que cumplen criterios de sepsis, presentan comorbilidad relevante, ancianos y en los inmunodeprimidos, portadores de neoplasias sólidas con o sin neutropenia [1,3-5].

En este escenario, entre el 1-3% de los pacientes que se atienden en los SUH lo hacen con el diagnóstico de una neoplasia sólida y, se conoce, que estas cifras también aumentan cada año [3,4]. Los pacientes con cáncer tienen hasta cuatro veces más probabilidades de presentar sepsis y bacteriemia en los SUH y la mortalidad a los 30 días de estos enfermos con bacteriemia verdadera (BV) confirmada desde el SUH supone el doble o el triple que el resto de pacientes con cáncer pero sin BV [1,3-6].

Los hemocultivos (HC) permiten el diagnóstico etiológico de la infección, aportan información sobre la sensibilidad del microorganismo y favorecen la optimización del tratamiento antimicrobiano [1,4,5]. Pero, la rentabilidad diagnóstica de los HC es muy variable (2-20%) [5] y su indicación para extraerlos en los SUH continua siendo controvertida, sobre todo en los pacientes más frágiles y vulnerables [7], donde el concepto de infección grave no se limita a la existencia de criterios de sepsis, también a la posible existencia de bacteriemia o neutropenia [8].

Por todo ello, la sospecha y confirmación de BV tiene un relevante significado diagnóstico, pronóstico y obliga a cambiar algunas de las decisiones a tomar en el SUH (alta o ingreso, extraer HC y administrar el antimicrobiano adecuado y precoz). Además, en el paciente con neoplasia sólida éstas adquieren una especial relevancia, ya que las manifestaciones clínicas son a menudo inespecíficas y variables, lo que dificulta su sospecha precoz y conlleva al fallo en el diagnóstico, en la solicitud de pruebas complementarias y, habitualmente, la administración de antimicrobianos no necesarios o su retraso en los casos donde sí son necesarios[1,3,8]. Así, en los últimos años se ha convertido en el objetivo de muchos autores elaborar modelos predictivos de BV identificables en los SUH que incluyen variables clínicas, epidemiológicas y analíticas [9,10]. Pero, son muy pocos los evaluados en pacientes con cáncer [9-11]. Precisamente, en estos pacientes con neoplasia, la sospecha de BV debe ser sospechada y confirmada con seguridad por su relevancia.

Recientemente, se ha publicado un nuevo modelo predictivo de bacteriemia (MPB-INFURG-SEMES) que consigue un área bajo la curva de la característica operativa del receptor (ABC-COR) de 0,924 y con 5 o más puntos una sensibilidad de 95,9%, especificidad de 76,2% y un valor predictivo negativo de 98,5% [12].

El objetivo de este estudio fue analizar la utilidad de dicho modelo en los pacientes con neoplasia sólida con sospecha de un proceso infeccioso en los SUH.

PACIENTES Y MÉTODOS

Estudio observacional de cohortes prospectivo y multicéntrico de los hemocultivos obtenidos de pacientes adultos (≥ 18 años) con neoplasia sólida atendidos en 63 SUH por un proceso infeccioso a los que se realizó un seguimiento durante 30 días y tras este periodo mantuvieron el diagnóstico de infección. Los centros participantes pertenecen al grupo INFURG-SEMES(Grupo de Infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias) (Ver adenda).

Desde el 1 de noviembre de 2019 al 31 de marzo de 2020 se incluyeron por oportunidad (cuando los investigadores estuvieron de guardia) los HC obtenidos de pacientes con neoplasia sólida diagnosticados de un proceso infeccioso en los que, como condición, también se registraron los datos de las siete variables del modelo "MPB-INFURG-SEMES". La indicación de la solicitud de HC se llevó a cabo según el criterio del médico responsable.

Para la elaboración y desarrollo de este estudio se asumieron y adoptaron todas las definiciones, criterios, técnicas, métodos establecidos para la recogida de muestras, valores de referencia y variables analizadas del estudio primigenio del MPB-INFURG-SEMES, y se reprodujeron y replicaron todos los aspectos metodológicos y de análisis estadístico contemplados en su elaboración [12]. Todos los pacientes tenían el diagnóstico confirmado de alguna neoplasia sólida y, entre ellos se clasificaron en subgrupos si tenían o no metástasis y neutropenia.

En primer lugar, para el análisis del comportamiento de la escala original, se construyó un sistema de puntuación de riesgo en el que se asignó una puntuación a cada variable del modelo MPB-INFURG-SEMES: temperatura >38,3°C (1 punto), índice de Charlson ≥3 (1 punto), frecuencia respiratoria ≥22 respiraciones por minuto (1 punto), un recuento de leucocitos >12.000/mm^3 (1 punto), trombopenia <150.000/mm^3 (1 punto), escalofríos-tiritona (1 punto), y una concentración de procalcitonina (PCT) ≥0,51 ng/ml (4 puntos) [12]. Así, se categorizó a los pacientes en once grupos (0-10 puntos) según el riesgo de BV para hacer recomendaciones diferentes en cada uno de ellos. La capacidad de discriminación del modelo predictivo se analizó calculando el ABC-COR y su intervalo de confianza al 95% (IC 95%). Se evaluó la calibración del modelo mediante la prueba de bondad de ajuste de Hosmer-Lemeshow. Posteriormente, se validó internamente el resultado obtenido mediante un análisis de remuestreo (*bootstrapping)* con 1.000 remuestreos y se calculó el ABC-COR y su IC 95%. Los errores estándar de las ABC se calcularon por métodos no paramétricos.

En segundo lugar, con el PC ≥5 puntos (el elegido en el estudio original) se calculó el rendimiento diagnóstico de este PC con su sensibilidad (S), especificidad (E), valor predictivo positivo (VPP) y el valor predictivo negativo (VPN). En todos los contrastes se rechazó la hipótesis nula con error α <0,5. El análisis

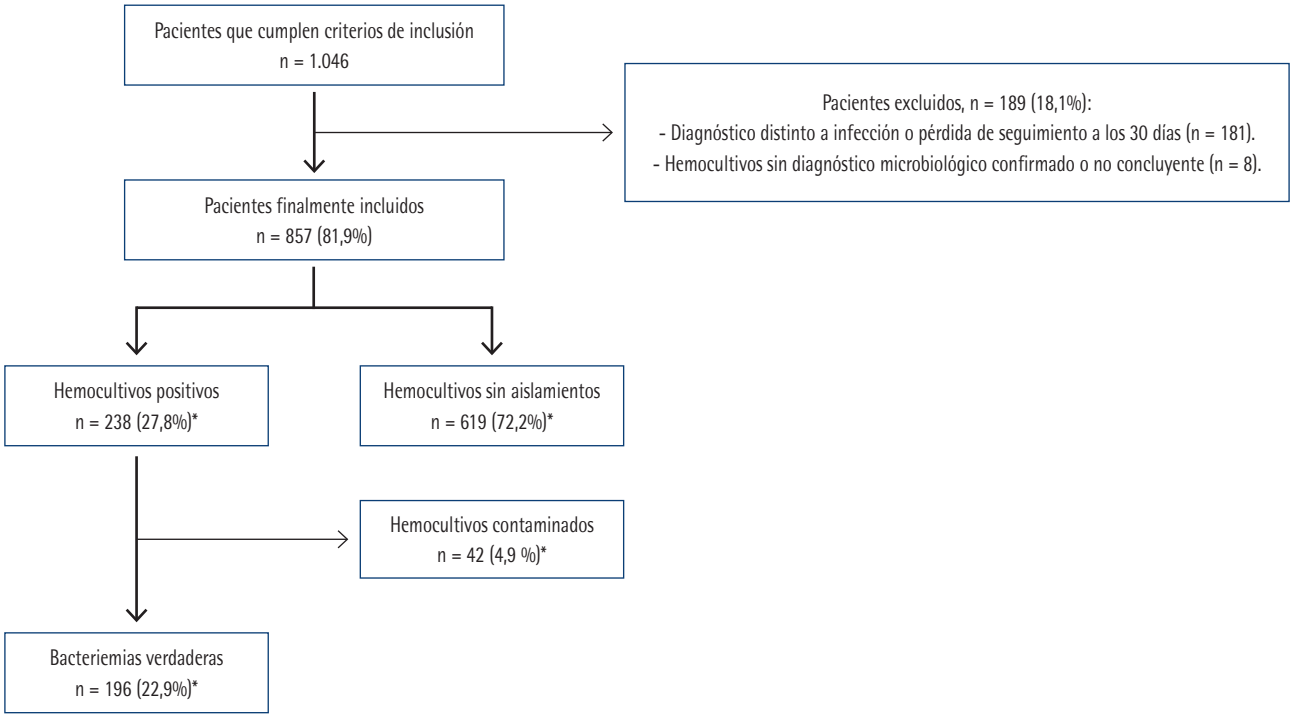


Figura 1 | **Diagrama de flujo de la inclusión de casos**

*** Porcentaje sobre el total de pacientes incluidos en el estudio (n = 857)**
Hemocultivos negativos 661 (77,1%): incluyen los 619 sin aislamiento y los 42 definidos como contaminados.

estadístico se realizó con los paquetes IBM-SPSS®Statistics24 para Windows y STATA.12.0.

El estudio siguió los protocolos de nuestros centros e internacionales (Declaración de Helsinki) y para la utilización de los datos de los pacientes que se codificaron para asegurar la confidencialidad de los mismos. El estudio fue aprobado por el Comité Ético de Investigación Clínica(CEIC) del Complejo Hospitalario Universitario de Toledo (Ref:398/2109), así como por los CEIC/CEIm de referencia de los centros participantes. Todos los pacientes dieron su consentimiento escrito para participar en el estudio.

RESULTADOS

Se incluyeron 857 episodios de HC extraídos. La edad media de los pacientes fue de 69,72 (DE 17,9) años, 607 eran varones (70,8%). De ellos, se consideraron como BV 196 y como HC negativos 661. Entre los negativos, 42 se consideraron contaminados (Figura 1). Finalmente, cabe señalar que 9 (4,6%) de las BV se confirmaron en pacientes dados de alta tras la valoración en el SUH o tras haber permanecido en observación unas horas.

En la Tabla 1 se muestran algunas de las características sociodemográficas, clínicas, epidemiológicas, comorbilidades, funcionales, clínicas, de gravedad, analíticas, de evolución y destino de los pacientes con los datos del estudio comparativo de los casos de BV frente a los HC negativos.

Las bacterias más frecuentemente aisladas fueron: i) Gramnegativas (103; 52,55%) con/sin resistencias (BLEE, carbapenemasas, multirresistente), entre ellas *Escherichia coli* en 52 HC (26,5%); *Klebsiella pneumoniae* en 13 (6,6%); y *Pseudomonas aeruginosa* en 11 HC (5,6%). ii) Grampositivas (93; 47,44%), entre ellas *Streptococcus pneumoniae* en 29 (14,8%); *Enterococcus* spp. en 17 (8,7%); *Staphylococcus aureus* meticilin sensible o resistente en 13 (6,6%).

El tipo u origen de tumor primario que presentaban los pacientes con BV era pulmón (59; 30,1%), mama (37; 18,9%), colorrectal (33; 16,8%), próstata (10; 5,1%), esofago-gástrico (10; 5,1%), laringe-faringe (7; 3,6%), pancreático (7; 3,6%), renal (6; 3,1%), hepático-biliar (6; 3,1%), ovario (5; 2,5%), sistema nervioso central (5; 2,5%), sarcomas (4; 2,0%), otros (7; 3,6%).

En la Figura 2 se muestra la imagen y el rendimiento diagnóstico (ABC-COR) de las muestras de todos los pacientes con tumor sólido, aquellos con metástasis y los que presentaban neutropenia en su visita al SUH, así como los datos comparativos con el ABC-COR del modelo original junto con los resultados de S, E, VPP y VPN del PC ≥ 5 puntos del MPB-INFURG-

Tabla 1 **Características clínico-epidemiológicas, de evolución, analíticas y de destino la muestra global y estudio univariable en función de la existencia o no de bacteriemia verdadera**

	Total n=857	BACTERIEMIA VERDADERA n=196 (22,9%)	HEMOCULTIVOS NEGATIVOS n=661 (77,1%)	Valor p
DATOS DEMOGRÁFICOS-EPIDEMIOLÓGICOS				
Edad (años), media (DE)	69,72 (13,25)	70,20 (13,30)	69,58 (13,2)	0,421
Edad ≥ 65 años, n (%)	563 (65,7)	128 (65,3)	435 (65,8)	0,480
Género masculino, n (%)	607 (70,8)	138 (70,4)	469 (71,0)	0,474
Institucionalizado, n (%)	45 (5,3)	11 (5,6)	34 (5,1)	0,458
Toma de AB en 72 horas previas, n (%)*	144 (38,3)	26 (31,7)	118 (40,1)	0,103
Ingreso en el último mes previo , n (%)	156 (18,2)	38 (19,4)	118 (17,9)	0,347
Portador de catéter central , n (%)	98 (11,4)	22 (11,2)	76 (11,5)	0,516
Portador de sondaje vesical, n (%)	98 (11,4)	32 (11,4)	66 (10,0)	0,012
COMORBILIDADES				
TS con metástasis, n (%)	279 (32,6)	66 (33,7)	213 (32,2)	0,383
TS con neutropenia, n (%)	80 (9,3)	22 (11,2)	58 (8,8)	0,184
Quimioterapia-inmunosupresores, n (%)	423 (49,35)	107 (54,59)	316 (47,80)	0,006
Enfermedad cardiaca crónica, n (%)	58 (6,8)	9 (4,6)	49 (7,4)	0,109
Enfermedad renal crónica, n (%)	95 (11,1)	32 (16,3)	63 (9,5)	0,007
Enfermedad cerebrovascular, n (%)	71 (8,3)	18 (9,2)	53 (8,0)	0,348
EPOC, n (%)	146 (17,0)	23 (11,7)	123 (18,6)	0,014
HTA, n (%)	395 (46,1)	90 (45,9)	305 (46,1)	0,511
Diabetes Mellitus, n (%)	177 (20,7)	43 (21,9)	134 (20,3)	0,239
Índice de Charlson[a] [media (DE)]	5,31 (2,63)	5,63 (2,58)	5,21 (2,65)	0,053
Índice de Charlson ≥ 3, n (%)	718 (83,8)	181 (92,3)	537 (81,2)	<0,001
Índice de Barthel[b] [media (DE)]	86,70 (26,16)	85,76 (24,95)	86,99 (26,52)	0,672
Índice de Barthel ≤ 60, n (%)	124 (15,0)	26 (13,7)	98 (15,4)	0,327
DATOS CLÍNICOS Y DE GRAVEDAD				
Temperatura en grados centígrados [media (DE)]	37,28 (8,16)	38,08 (1,15)	37,05 (125)	0,005
Temperatura > 38,3°C, n (%)	270 (31,6)	99 (50,5)	171 (26,0)	<0,001
FC en lpm [media (DE)]	101,01 (20,22)	105,87 (23,25)	99,57 (19,02)	<0,001
FC > 90 lpm, n (%)	598 (71,0)	151 (77,04)	447 (67,7)	0,004
FR en rpm [media (DE)]	21,84 (7,24)	25,16 (8,98)	20,39 (6,56)	<0,001
FR ≥ 22 rpm, n (%)	310 (39,3)	121 (62,1)	189 (31,9)	<0,001
Alteración de la consciencia ECG ≤ 14, n (%)	126 (15,0)	42 (21,8)	84 (13,0)	0,003
PAS en mmHg [media (DE)]	117,97 (27,30)	109,70 (25,84)	120,44 (27,26)	<0,001
PAS < 100 mmHg, n (%)	241 (28,5)	78 (40,0)	163 (25,0)	<0,001
Criterios de sepsis (SRIS ≥ 2), n(%)	568 (66,3)	163 (83,2)	405 (61,3)	<0,001
Criterios shock séptico (Sepsis-2), n (%)	138 (16,5)	59 (31,1)	79 (12,2)	<0,001
qSOFA ≥ 2, n(%)	157 (18,3)	66 (33,7)	91 (13,8)	<0,001
Criterios Shock séptico (Sepsis-3), n (%)	93 (11,1)	48 (25,0)	45 (7,0)	<0,001
Escalofríos-tiritona, n (%)	415 (49,0)	131 (67,9)	284 (43,4)	<0,001

Tabla 1 **Características clínico-epidemiológicas, de evolución, analíticas y de destino la muestra global y estudio univariable en función de la existencia o no de bacteriemia verdadera (cont.)**

	Total n=857	BACTERIEMIA VERDADERA n=196 (22,9%)	HEMOCULTIVOS NEGATIVOS n=661 (77,1%)	Valor p
HALLAZGOS DE LABORATORIO				
Leucocitos por mm^3 [media (DE)]	12.047 (10.906)	13.565 (9.757)	11.592 (11.193)	0,007
Leucocitosis > 12.000/mm^3, n (%)	524 (61,1)	144 (73,5)	380 (57,5)	<0,001
Cayados (bandas) > 10%, n (%) *	45 (7,8)	21 (15,2)	24 (5,5)	<0,001
Plaquetas por mm^3 [media (DE)]	211.160 (125.693)	173.960 (105.136)	222.180 (129.194)	<0,001
Trombopenia < 150.000/mm^3, n (%)	257 (29,9)	81 (41,32)	176 (26,6)	<0,001
Procalcitonina en ng/ml [media (DE)]	3,52 (10,57)	10,38 (16,71)	1,49 (6,65)	<0,001
Procalcitonina ≥ 0,51 ng/ml, n (%)	310 (36,2)	189 (96,4)	121 (18,3)	<0,001
Proteína C reactiva en mg/l [media (DE)]	19,22 (13,35)	23,81 (15,37)	18,43 (12,77)	<0,001
Proteína C reactiva ≥ 9 mg/l, n (%) *	494 (63,3)	121 (66,5)	373 (62,3)	0,173
Lactato sérico en mmol/l ([media (DE)]	2,83 (2,98)	3,62 (3,09)	2,58 (2,90)	<0,001
Creatinina ≥ 2 mg/dl, n (%)	138 (16,1)	61 (31,1)	77 (11,6)	<0,001
DATOS DE EVOLUCIÓN Y DESTINO				
Días desde inicio de la clínica [media (DE)]	3,04 (4,64)	2,58 (4,01)	3,17 (4,80)	0,089
Destino inicial de los pacientes				<0,001
Alta	137 (15,9)	9 (4,6)	128 (19,4)	
Planta de hospitalización	656 (76,5)	153 (78,1)	503 (76,1)	
Unidad de Cuidados Intensivos	55 (6,4)	30 (15,3)	25 (3,8)	
Fallecimiento en urgencias	9 (1,1)	4 (2,0)	5 (0,8)	
Estancia hospitalaria en días [media (DE)]	11,83 (9,24)	14,65 (10,31)	10,50 (9,35)	<0,001
Mortalidad a los 30 días	161 (18,8)	51 (26,0)	110 (16,6)	0,001

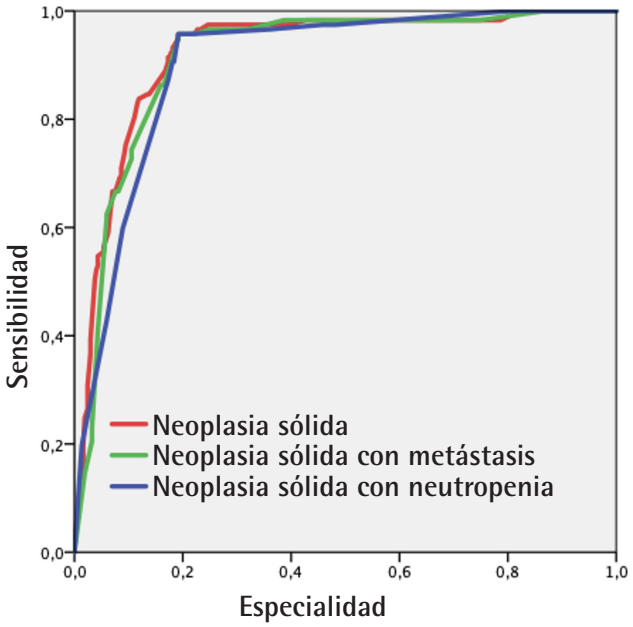
Hemocultivos negativos 661: incluyen los 619 sin aislamiento y los 42 definidos como contaminados.
DE: desviación estándar; n: número; AB: antibióticos; TS: Tumor sólido; EPOC: Enfermedad pulmonar obstructiva crónica; HTA: hipertensión arterial; C: centígrados; FC: frecuencia cardiaca; lpm: latidos por minuto; FR: frecuencia respiratoria; rpm: respiraciones por minuto.
*** No se incluyen los valores perdidos. [a]Índice de Charlson (A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis. 1987;40:373-83). [b]Índice de Barthel (Functional evaluation: The Barthel Index. Md State Med J. 1965;14:61-5).**
Criterios de sepsis (SRIS ≥ 2) según conferencia de Consenso de 2001 (Sepsis-2) [1]
Criterios de sepsis (qSOFA ≥ 2) según la tercera conferencia de consenso (Sepsis-3) [1]

SEMES. El ABC-COR del modelo para los pacientes con tumor sólido fue de 0,923(IC 95%:0,896-0,950;p<0,001). El test de bondad de ajuste de Hosmer-Lemeshow presentó un valor de p de 0,568. La validación interna, mediante la técnica de remuestreo *(bootstrapping)* fue de 0,908 (IC 95%:0,881-0,935).

DISCUSIÓN

Los resultados de este estudio permiten confirmar la utilidad de un novedoso modelo de riesgo para predecir bacteriemia en los pacientes con neoplasia sólida, con o sin neutropenia, atendidos en los SUH por un proceso infeccioso. La recientemente publicada escala de puntuación MPB-INFURG-SEMES [12] (que tiene una calculadora on-line disponible en: https://mpbscore.urgenciasclinico.com), incluye variables obtenibles en el primer momento de la atención de los pacientes con sospecha de infección grave: exploratorias (temperatura, frecuencia respiratoria y escalofríos-tiritona), de comorbilidad (índice de Charlson) y analíticas (recuento de leucocitos y plaquetas y concentración sérica de PCT).

Por lo tanto, puede representar una útil herramienta de ayuda a la hora de predecir la existencia de BV en los pacientes con neoplasias sólidas (con/sin neutropenia), uno de los grupos más vulnerables y con una frecuente presentación clínica inespecífica [3,4,13], para así optimizar las decisiones más importantes e inmediatas que se deben tomar en los SUH: indicación de extracción de HC, administrar una terapia antimicrobiana adecuada y precoz y el ingreso hospitalario o el alta domiciliaria, entre otras [1,13,14].



MPB-INFURG-SEMES Punto de corte ≥ 5 puntos	ABC-COR (IC 95%)	Sensibilidad % (IC 95%)	Especificidad % (IC 95%)	VPP % (IC 95%)	VPN % (IC 95%)
MPB-INFURG-SEMES artículo original	0,924 (0,916-0,933) p < 0,001	95,94 (95,46 - 96,42)	76,28 (75,8 - 76,76)	53,63 (53,15 - 54,11)	98,50 (98,02 - 98,98)
En pacientes con neoplasia sólida	0,923 (0,896-0,950) p < 0,001	95,74 (94,92 - 96,56)	76,06 (75,24 - 76,88)	53,42 (52,60 - 54,24)	98,48 (97,66 - 99,30)
En pacientes con neoplasia sólida con metástasis	0,914 (0,885-0,942) p < 0,001	96,23 (95,61 - 96,85)	76,24 (75,62 - 76,86)	51,96 (51,34 - 52,58)	99,24 (98,62-99,70)
En pacientes con neoplasia sólida con neutropenia	0,904 (0,875-0,932) p < 0,001	98,17 (96,56-99,78)	80,38 (78,77-81,99)	60,98 (59,37-62,59)	99,68 (98,07-99,98)

Figura 2 | **Rendimiento para la predicción de bacteriemia verdadera del MPB-INFURG-SEMES en los hemocultivos extraídos en urgencias**

MPB-INFURG-SEMES: modelo de predicción de bacteriemia INFURG-SEMES (Referencia 12)
IC 95%: intervalo de confianza al 95%; ABC-COR: área bajo la curva de la característica operativa del receptor;
VPP: valor predictivo positivo; VPN: valor predictivo negativo

El muy buen rendimiento pronóstico de BV en los pacientes con neoplasia sólida, con un ABC-COR obtenida de 0,923, así como en el subgrupo de pacientes con neutropenia (de 0,904; discretamente inferior) similar a la publicada del modelo original de 0,924 [12] y al único artículo publicado que valida y confirma la utilidad del modelo MPB-INFURG-SEMES en pacientes atendidos en los SUH [15], permite clasificar a todos los pacientes en 11 grupos de riesgo (de 0 a 10 puntos), donde el PC ≥5 puntos obtiene una S:95,74%, E:76,06% y un VPN:98,48%, lo que puede representar una ayuda evidente para descartar la existencia de BV en aquellos pacientes con neoplasias sólidas y neutropenia en el SUH. Por ello, en los pacientes con neoplasia sólida en los que se confirmen 5 o más puntos aplicando la escala de puntuación MPB-INFURG-SEMES [12], siempre deberíamos sospechar la existencia de BV y, tras extraer HC, actuar como si existiera hasta confirmar o descartar el crecimiento de patógenos en los HC. Y, en el caso del subgrupo de pacientes con neoplasia sólida y neutropenia en el SUH, al menos hasta que existan otros estudios de validación, la extracción de HC y necesidad de descartar BV, debería ser más flexible e individualizada.

Aunque la técnica de extracción de los HC está bien protocolizada [16], todavía existen controversias en relación a cuándo debemos obtenerlos en el SUH [1,8,13]. A pesar de ello, es una práctica creciente en la valoración inicial de los pacientes con cáncer y sospecha de infección en el SUH [1-3,5]. En estos, la sospecha de bacteriemia tiene un importante significado diagnóstico y pronóstico. Pero, además, los HC también se ob-

tienen en el SUH como garantía de continuidad asistencial, ya que del conocimiento de sus resultados dependerá el manejo y evolución posterior del paciente en su destino final [1,8,13,14].

En este escenario, en los últimos años, se ha acentuado el estudio de los factores predictores de bacteriemia (precisamente la existencia de neoplasia se ha confirmado como uno de ellos [6]) y se han propuesto distintos modelos predictivos para los SUH de distinta complejidad que podemos encontrar en recientes revisiones [9,10], una de ellas sistemática [11], aunque muy escasos en relación específica con los pacientes oncológicos [9-11]. Entre estos factores predictores, ha adquirido una gran relevancia el papel que pueden jugar los biomarcadores, y en especial la PCT [9-11,17,18], como factores predictores independientes de bacteriemia. Se ha demostrado que su capacidad diagnóstica puede igualar, e incluso superar, la de distintos modelos, incluyendo el más utilizado, conocido y validado en la última década (modelo de Shapiro *et al.* [19]). En este sentido, estas recientes revisiones han mostrado la mayor capacidad de los nuevos modelos que incluyen la PCT (5MPB-Toledo y el propio MPB-INFURG-SEMES) sobre el resto, recomendándose su uso para los pacientes atendidos en los SUH [9-11]. Aunque, también en ellas se señalaba la necesidad de disponer de estudios de validación en subgrupos de pacientes como los ancianos o los pacientes con inmunodepresión para el MPB-INFURG-SEMES, como lo pueden ser los de nuestra muestra, tal y como si se ha hecho anteriormente con el 5MPB-Toledo [20]. Aunque, afortunadamente en España ya la gran mayoría de los SUH tienen disponibilidad de solicitar PCT [21,22], es cierto que el Latinoamérica, hoy en día más del 50% no tienen disponibilidad de utilizar la PCT. Esta realidad supone una limitación de su posible puesta en práctica.

Nuestro estudio presenta algunas limitaciones: la indicación de solicitar HC se realiza según las decisiones del médico responsable, los casos fueron incluidos por oportunidad(cuando los investigadores estuvieron de guardia) o la tasa de HC contaminados (4,9%), aunque menor que en estudios realizados en nuestro medio, sí es superior a la recomendada (< 3%) [5,6,15,16]. No obstante, creemos que los resultados representan un fiel reflejo de la realidad de nuestros SUH donde la incidencia de pacientes con neoplasia sólida y neutropenia es muy importante cuantitativa y cualitativamente [1-3].

En conclusión, el modelo MPB-INFURG-SEMES podría ser de utilidad para la estratificación de riesgo de bacteriemia en los pacientes con tumor sólido(con/sin neutropenia) atendidos en el SUH. Ya que es capaz de predecirla adecuadamente con variables fácilmente disponibles y, junto al juicio clínico y otras variables independientes del proceso y del paciente, facilita la toma de decisión de indicación de obtención de HC en los SUH y la estrategia diagnóstico-terapéutica.

ADENDA

Otros miembros del grupo INFURG-SEMES (Grupo de Infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias) participantes en el estudio: Itziar Huarte Sanz, Esperanza Ansa Arlegui, Igor Gallastegi Ruiz de Egino, Ricardo Palenzuela Arozena, Nerea Sarriegi Gorrotxategi, Xabier Errazkin Telletxea, Laura Munguía Nieva, Diego Vicente Anza , Maitane Arrastia Erviti (*Hospital Universitario de Donosti*); Carmen Navarro Bustos, Isabel María Morales Barroso, María Carmen Manzano Alba, Fernando Oltra Hostalet, José Gallardo Bautista, María Angustias Sevilla Espejo (*Hospital Virgen de la Macarena de Sevilla*); Isabel Nieto Rojas, Elena Sánchez Maganto, Raúl Canabal Berlanga, Pedro Beneyto Martín (*Complejo Hospitalario Universitario de Toledo*); Pablo Jerez-Fernández, Miguel Suarez- Robles, Clara Ramos-Rey, Ines Armenteros Yeguas, María Fernández-Revaldería, Eva Orviz García, Francisco Javier Martín Sánchez (*Hospital Universitario Clínico San Carlos de Madrid*); Josep María Guardiola Tey, Leopoldo Higa Sansone, Marta Blazquez Andion, Miriam Mateo Roca, Sergio A. Herrera Mateo (*Hospital de Sant Pau de Barcelona*); Marta Álvarez Alonso, María Jesús Domínguez García, Ma Eugenia Barrero Ramos, Cristina Latorre Marco , Gema Delgado Cárdenas, Alberto Sánchez Bernal, Ángela Flores Palacio, Laura Martínez Vega, Laura Pérez Calero, Teresa Rincón Sánchez (*Hospital Universitario de Fuenlabrada*); Begoña Mora Ordoñez, M. Lourdes Nieto de Haro, Jerónimo Amores Fernández (*Hospital Virgen de la Victoria de Málaga*); Oscar Álvarez López Silvia Álvarez Kailis, Beatriz Paderne Díaz, Gema María Gómez García, Alicia Rodríguez Urgel (*Hospital Universitario de Móstoles*), Ferrán Llopis-Ro- ca, Sebastià Quetglas Roselló, Manel Tuells Morales, Marta Maristany Bosch, Ana Badía Tejero (*Hospital Universitario de Bellvitge*); Mar Ortega Romero, Omar Saavedra, Nuria Seguí, Leticia Fresco, Gina Osorio, Julia Calvo, Joan Ribot, Irene Carbonell (*Hospital Clínic de Barcelona*), Esperanza Puga Montalvo, Ziad Issa-Masad Khozouz (*Hospital Campus de la Salud de Granada*), Ramón Perales Pardo, Katia Chávez Tafur, Yolanda Prieto Corredor, Consuelo Parra Carretero, Mercedes Elena Pina (*Complejo Hospitalario Universitario de Albacete*); Mikel Martínez-Ortiz de Zarate, Idoia Madariaga Ordeñana, Ainhoa Burzako Sánchez, (*Hospital Universitario de Basurto*); María José Marchena González, Esther Maldonado Pérez, Rocío Garrido Rasco, Miguel Albarrán Núñez (*Hospital Juan Ramón Jiménez de Huelva*); María del Mar Sousa Reviriego, Alicia Beteta López, Laura Janeth Duran Ducón, Sandra Verónica Tarabó Mieles, Ricardo Juárez González (*Hospital Nuestra Señora del Prado de Talavera*); José María Ferreras Amez (*Hospital Clínico Universitario Lozano Blesa de Zaragoza*); Henrique Villena García del Real (*Complejo Hospitalario Universitario de Santiago de Compostela*); Belén Arribas Entrala (*Hospital Universitario Miguel Servet de Zaragoza*), Marta Honrado Fernández de Valderrama (*Hospital Santiago Apóstol de Miranda de Ebro*), Eva Quero Motto, Eva Mónico Castillo, Antonia Cantero Sandoval, Roxana Rojas Luán, María Jesús Huertas Sánchez (*Hospital Virgen de la Arrixaca de Murcia*); Agustín Arévalo Velasco, M. Jesús Bringas García, Ángel García García, Carmen Rivas Herrero, Sonia Del Amo Diego (*Complejo Asistencial Universitario de Salamanca*); Manel R. Chanovas-Borràs, Manuel Martínez Maimó, Noelia Cases Ariño, Carmen Melinda Prica, Montserrat Pech Solà (*Hospital Verge de la Cinta de Tortosa*); María Bóveda García, Jessica Mansilla Collado, Leticia Serrano Lázaro, Javier Millán Soria (*Hospital La Fe de Valencia*); Pascual Piñera

Salmerón, Sergio Pastor Marín, Elena del Carmen Martínez Cánovas, Gaelia Bornas Cayuela, Alba Hernández Sánchez, José Andrés Sánchez Nicolás (*Hospital Universitario Reina Sofía de Murcia*); Ángel Estella García, Mariola Aguilera Vidal, Mónica Carlota Aguilera Casasola, María del Mar Luque de Igunza, María Cristina Martín Rodríguez (*Hospital Universitario de Jerez*); Octavio José Salmerón Béliz, Ana Mecina Gutiérrez, Marta Beneyto Arana, Olivia Devora Ruano, Mª. Mar Bermejo Olano (*Hospital Universitario Fundación de Alcorcón*), Guillermo Burillo Putze, Aarati Vaswani-Bouchald, Carmen Mercedes García-Pérez, Carmen de la Fuente-García, Jazael Santana Rodríguez (*Hospital Universitario de Canarias*); Ester Monclús Cols, María Jové Lázaro, David Pellejà Monné, María Mercedes Brea Álvarez (*Hospital Sant Jaume de Calella de Barcelona*); Marta Balaguer Catalán, Teresa López Fernández, Noelia Orts Saurí, Alberto Cercós Perez, María Luisa López Grima (*Hospital Universitario Doctor Peset de Valencia*); Manuel Gil Mosquera, Luis Pérez Ordoño, Natalia Sánchez Prida, Laura Santos Franco, María Eugenia García Gil (*Hospital Universitario 12 de octubre de Madrid*); Félix González Martínez, Diana Moya Olmeda, María José Rodríguez Escudero (*Hospital Virgen de la Luz de Cuenca*); Ainhoa Urraca Gamaury, Marta Abeijón Vila, Carlos Aldasoro Frías (*Complejo Asistencial de Zamora*); Jesús Álvarez-Manzanares, Raúl López Izquierdo, Nieves Sobradillo Castrodeza (*Hospital Universitario Río Hortega de Valladolid*); Luis Quero Reboul (*Hospital Virgen de la Merced de Osuna*); Agurtzane Auzmendi Aguirre (*Hospital de Mendaro de Gipuzkoa*); Federico Melgosa Latorre, Fernando Abadia Cebrian, Ainhoa Albizuri Bernaola (*Hospital de Alto Deba de Arrasate*); Francisco José Ezponda Inchauspe, Ana María Iturzaeta Gorrotxategi (*Hospital de Zumárraga*); Pilar Jiménez (*Hospital de Antequera*); Josefina Monedero La Orden, Fernando Constantino Briones Monteagudo, Luis Miguel Cruz Ramírez (*Hospital de Almansa*); Ariel Ruben Lindo Noriega, Miguel Ángel Callejas Montoya, Gonzalo Fuentes Rodríguez (*Hospital de Villarrobledo*); Marta Iglesias Vela, Susana García Escudero, Nuria Álvarez Díez (*Complejo Asistencial Universitario de León*); Inmaculada Adán Valero, Pilar Yagüe Gómez, Jorge Eduardo Toledo Toledo (*Hospital de Valdepeñas*); Julio Javier Gamazo-Del Rio (*Hospital Universitario de Galdakao-Usansolo*); Belén Rodríguez (*Hospital Universitario Rey Juan Carlos*); Francisco J. Aramburu, Oscar Pérez Carral, Natalia Catherine Franco Zárate (*Complejo Hospitalario Universitario de Ourense*); Bárbara Díaz García, María José del Río Paz, Sonia Beatriz Rodríguez Martínez (*Hospital de Barbanza*); Virginia Álvarez Rodríguez, Eduardo Manzone, Rodolfo Romero Pareja (*Hospital Universitario de Getafe*); Ángel José Macías López, Antón Trigo González, Ángel Francisco Viola Candela (*Complejo Asistencial de Ávila*); María Debán Fernández, Pablo Herrero Puente (*Hospital Central de Asturias*); Fernando Rodríguez Pérez-Reverte, Ascensión Martínez Más, Sofía Martínez Saldumbide (*Hospital Universitario Santa Lucía de Cartagena en Murcia*); Neus Robert, Adrià Mendoza, Arantzazu Blanco (*Hospital de Can Ruti*); Silvia Flores Quesada, Osvaldo Troiano Ungerer (*Hospital San Pau i Santa Tecla de Tarragona*); Rosa García García, Fátima González Jiménez, Sara Moreno Suarez (*Hospital Virgen de las Nieves de Granada*); Raquel Rodríguez Calveiro, Inés López Fernández (*Hospital Alvaro Cunqueiro de Vigo*); Manuel García Novio, Teresa Pajares Vázquez (*Hospital Universitario Lucus Augusti de Lugo*); Laura González González (*Hospital del Salnes de Vilagarcía de Arousa*); Elena Carrasco Fernández (*Hospital Virgen De Altagracia de Manzanares*); María Pilar Lozano García, Daniela Mihaela Comaneci (*Hospital Universitario de Guadalajara*); Rigoberto Del Rio Navarro, Guillermo Moreno Montes (*Hospital de Torrevieja*); Elizabeth Ortiz García (*Hospital Santa Bárbara de Soria*); Leopoldo Sánchez Santos (*Hospital Universitario de Burgos*); Rosario Peinado (*Hospital Infanta Cristina de Badajoz*); Beatriz Valle Borrego (*Hospital Severo Ochoa de Leganés*); Pablo Javier Marchena Yglesias (*Parc Sanitari Sant Joan de Déu de Sant Boi de Llobregat*); Cristina Herranz Martínez (*Hospital de Viladecans de Barcelona*); Núria Pomares, Xavier López Altimirias (*Fundació Hospital de Mollet*).

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CONFLICTO DE INTERESES

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BIBLIOGRAFÍA

1. Julián-Jiménez A, Supino M, López Tapia JD, Ulloa González C, Vargas Téllez LE, González del Castillo J, et al. Puntos clave y controversias sobre la sepsis en los servicios de urgencias: propuestas de mejora para Latinoamérica. Emergencias 2019;31:123-135. PMID: 30963741
2. Julián-Jiménez A. Hacia la normalización en la atención a los pacientes con COVID-19 en urgencias. Emergencias. 2023;35:321-2. PMID: 37801411
3. Fleshner L, Lagree A, Shiner A, Alera MA, Bielecki M, Grant R, et al. Drivers of Emergency Department Use Among Oncology Patients in the Era of Novel Cancer Therapeutics: A Systematic Review. Oncologist. 2023;28:1020-1033. doi: 10.1093/oncolo/oyad161. PMID: 37302801.
4. Hsu J, Donnelly JP, Moore JX, Meneses K, Williams G, Wang HE. National characteristics of Emergency Department visits by patients with cancer in the United States. Am J Emerg Med. 2018;36:2038-2043. doi: 10.1016/j.ajem.2018.03.025. PMID: 29573899.
5. Rubio Díaz R, Nieto Rojas I, Julián-Jiménez A. Importancia de los resultados de los hemocultivos: especial atención para los solicitados desde los Servicios de Urgencias. Rev Esp Quimioter. 2020;33:459-61. doi: 10.37201/req/075.2020
6. Zafar Iqbal-Mirza S, Estévez-González R, Serrano-Romero de Ávila V, De Rafael González E, Heredero-Gálvez E, Julián-Jiménez A. Fac-

tores predictores de bacteriemia en los pacientes atendidos en el Servicio de Urgencias por infección. Rev Esp Quimioter 2020;33: 32-43 doi: 10.37201/req/075.2019

7. Aguiló Mir S. Identificar al paciente frágil en un servicio de urgencias: un esfuerzo urgente y necesario. Emergencias. 2023;35:165-6. PMID: 37350598
8. Julián-Jiménez A, Gorordo-Delsol LA, Merinos-Sánchez G, Santillán-Santos DA, Rosas Romero FA, Sánchez Arreola D, et al. Declaración de Guadalajara: una visión constructiva desde el servicio de urgencias a partir de la Surviving Sepsis Campaign 2021. Emergencias. 2023;35:53-64. PMID:36756917
9. Clemente-Callejo C, Julián-Jiménez A, Candel González FJ, González del Castillo J. Models for bacteraemia risk prediction. Clinical implications. Rev Esp Quimioter 2022; 35 (Suppl. 3): 89-93 doi: 10.37201/req/s03.19.2022. PMID: 36285866
10. Julián-Jiménez A, Rubio-Díaz R, González del Castillo J, Candel González FJ. New predictive models of bacteremia in the emergency department. Rev Esp Quimioter. 2022;35:344-356. doi:10.37201/req/015.2022 PMID: 35413783
11. Julián-Jiménez A, García DE, García de Guadiana-Romualdo L, Merinós-Sánchez G, Candel González FJ. Modelos predictivos de bacteriemia en el servicio de urgencias: revisión sistemática. Emergencias 2024;36:48-62. PMID: 38318742.
12. Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, Rubio Díaz R, et al; INFURG-SEMES investigators. A bacteraemia risk prediction model: development and validation in an emergency medicine population. Infection. 2022;50:203-221. doi: 10.1007/s15010-021-01686-7.
13. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063-e1143.
14. Julián-Jiménez A, García DE, González Del Castillo J, López Tapia JD. De la guías internacionales "Campaña para sobrevivir a la sepsis 2021" a las guías para "Detectar, prevenir la progresión y atender a los pacientes con infección grave en urgencias" elaboradas por urgenciólogos. Emergencias. 2022;34:471-3. PMID: 36625699.
15. Nieto Rojas I, López Forero WE. Improved profitability and indications for blood culture extraction in emergency departments: another step forward. Rev Esp Quimioter. 2023;36:97-98. doi:10.37201/req/075.2022
16. Guna Serrano MR, Larrosa Escartín N, Marín Arriaza M, Rodríguez Díaz JC. Diagnóstico microbiológico de la bacteriemia y fungemia: hemocultivos y métodos moleculares. Enferm Infecc Microbiol Clin. 2019;37:335-40. doi: 10.1016/j.eimc.2018.03.005
17. Rubio-Díaz R, Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, et al. Capacidad del lactato, procalcitonina y de los criterios definitorios de sepsis para predecir mortalidad a 30 días, bacteriemia o infección confirmada microbiológicamente en los pacientes atendidos por sospecha de infección en urgencias. Emergencias. 2022;34:181-9. PMID: 35736522
18. Julián-Jiménez A, García DE, Merinós-Sánchez G, García de Guadiana-Romualdo L, González del Castillo J. Precisión diagnóstica de la procalcitonina para la bacteriemia en el servicio de urgencias: una revisión sistemática. Rev Esp Quimioter. 2024;37(1):29-42. doi: 10.37201/req/099.2023
19. Shapiro N I, Wolfe R E, Wright S B, Moore R, Bates D W. Who needs a blood culture? A prospectively derived and validated prediction rule. J Emerg Med 2008; 35: 255-64. doi: 10.1016/j.jemermed.2008.04.001. PMID: 18486413.
20. Julián-Jiménez A, García-Lamberechts EJ, González Del Castillo J, Navarro Bustos C, Llopis-Roca F, Martínez-Ortiz de Zarate M, et al. Validation of a predictive model for bacteraemia (MPB5-Toledo) in the patients seen in emergency departments due to infections. Enferm Infecc Microbiol Clin. 2022;40:102–112. doi: 10.1016/j.eimce.2021.12.006. PMID: 34992000.
21. Llopis-Roca F, López Izquierdo R, Miro O, García- Lamberechts JE, Julián-Jiménez A, González del Castillo J. Mapa de la situación actual de la atención a la sepsis en los servicios de urgencias españoles. Rev Esp Quimioter 2022;35: 192-203. doi: 10.37201/req/150.2021. PMC8972694
22. De Santos Castro PÁ, Alonso Avilés R. On the ability of lactate, procalcitonin, and criteria defining sepsis to predict 30-day mortality, bacteremia, and microbiologically confirmed infection in patients with suspected infection treated in emergency departments. Emergencias. 2022;34:406. PMID: 36217940.

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Abrar Senhaji-Kacha[1,2*]
Arij Akir[1*]
Antonio Broncano-Lavado[1]
Jaime Esteban[1,2]

Biofilm prevention concentration of clarithromycin against clinically relevant species of nontuberculous mycobacteria

[1]Department of Clinical Microbiology, IIS-Fundación Jiménez Díaz, UAM, Madrid, Spain.
[2]CIBERINFEC-CIBER of Infectious Diseases, Madrid, Spain.

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ABSTRACT

Introduction. *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* are a group of nontuberculous mycobacteria (NTM) that have been described as human pathogens. Their ability to develop biofilms in tissues and medical devices is one of the most important pathogenicity factors, with important implications in diagnosis and treatment. Macrolides are usually considered one of the bases of this treatment.

Methods. Here we have studied the biofilm prevention concentration (BPC) of 16 strains (n=16) with clarithromycin to avoid the biofilm development by these NTM.

Results. In this study, all *M. abscessus* strains have similar BPC, while MAC strains showed different values. For MAC the concentrations ranged between 1-16 mg/L, while for *M. abscessus* the concentration was 32 mg/L for all strains except one that was 64 mg/L.

Conclusions. These results open the possibility of using macrolides for the prevention of biofilm development in patients with a risk of developing NTM disease.

Keywords: nontuberculous mycobacteria, BPC, MIC, biofilm prevention, *Mycobacterium abscessus*, *Mycobacterium avium*, clarithromycin.

Eficacia de la claritromicina contra el biofilm de especies clínicamente relevantes de micobacterias no tuberculosas

RESUMEN

Introducción. *Mycobacterium avium* complex (MAC) y *Mycobacterium abscessus* son un grupo de micobacterias no tuberculosas (NTM) que han sido descritas como patógenos humanos. Entre los factores de patogenicidad más importantes se encuentra su capacidad para desarrollar biopelículas en tejidos y dispositivos médicos, con importantes implicaciones en el diagnóstico y tratamiento. Los macrólidos suelen considerarse una de las bases de este tratamiento.

Métodos. En este estudio hemos estudiado la concentración para la prevención de biopelículas (BPC) de 16 cepas (n=16) con claritromicina para varias de estas NTM.

Resultados. Todas las cepas de *M. abscessus* tienen BPC similares, mientras que las cepas de MAC mostraron valores diferentes. Para MAC las concentraciones presentaron un rango entre 1-16 mg/L, mientras que para *M. abscessus* la concentración fue de 32 mg/L para todas las cepas excepto una, que fue de 64 mg/L.

Conclusiones. Estos resultados abren la posibilidad de utilizar macrólidos para la prevención del desarrollo de biopelículas en pacientes con riesgo de desarrollar enfermedad por NTM.

Palabras clave: micobacterias no tuberculosas, BPC, CMI, prevención de biopelículas, *Mycobacterium abscessus*, *Mycobacterium avium*, claritromicina.

INTRODUCTION

Nontuberculous mycobacteria (NTM) include the majority of the species of the genus *Mycobacterium*, including human pathogens such as *Mycobacterium abscessus* and *M. avium* complex. The *Mycobacterium avium* complex (MAC) includes three species that are a cause of human infections (*Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*), and are considered the commonest NTM isolated in humans throughout the world [1]. Infections caused by MAC are usually respiratory infections among patients with different comorbidities, while they can cause many different syndromes, including disseminated disease [2].

Correspondence:
Jaime Esteban, MD, PhD.
Department of ClinicalMicrobiology. IIS-Fundación Jiménez Díaz.
Av. Reyes Católicos, 2. 28040-Madrid, Spain.
E-mail: jestebanmoreno@gmial.com; jesteban@fjd.es

*These authors contributed equally to this manuscript and must be considered as first authors.

On the other hand, *Mycobacterium abscessus* is included among rapidly growing mycobacteria and is found with increasing frequency as an opportunistic human pathogen [3]. Although its taxonomy remains under debate, a widespread taxonomic classification divided this species into three subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, and *M. abscessus* subsp. *massiliense* [4]. Infections caused by these species are usually chronic and associated with immunological deficiencies, such as cystic fibrosis (CF), in which morbidity and mortality are associated with both infections and unusual immune responses [5].

NTM infections are currently considered biofilm-related infections, and this fact is of clinical importance because of the higher resistance against antibiotics of sessile bacteria compared with that of planktonic ones [6]. Therefore, avoiding biofilm formation could be extremely important for the management of the patients because it potentially can avoid the development of the disease or, at least, facilitate their treatment.

This study aimed to know the biofilm prevention concentration (BPC) of clarithromycin (an antibiotic that is considered a keystone in the treatment of NTM diseases) and compare it with the minimal inhibitory concentration of planktonic cells and antimicrobial susceptibility testing using *M. avium* complex and *M. abscessus* collection and clinical strains (n=16) isolated from patients with and without respiratory disease.

MATERIAL AND METHODS

Bacterial strains. A total of 16 strains (n=16) were used in this study. MAC strains used in this study were a total of nine including three type strains and two clinical strains of each species. *M. abscessus* strains used in this study were a total of seven including two type strains and five clinical strains (Table 1). The strains 330 and 624 showed a rough phenotype, while the strains 368, 611, and 531 have a smooth phenotype. The clinical significance of the clinical strains was determined according to the ATS-ERS-IDSA-ESCMID criteria [2], being clinically significant the strains *M. avium* 647, *M. intracellulare* 657, *M. chimaera* 655, and all the clinical strains of *M. abscessus*.

All strains were maintained at -80ºC and defrosted before performing the experiments, inoculated onto Middlebrook 7H10 agar (Difco™) plates supplemented with 10% Middlebrook OADC enrichment and 0.4% glycerol and incubated at 37ºC for 10-15 days. After 24h plates were checked for purity.

Antimicrobial susceptibility of planktonic bacteria. The studied clinical strains were tested for antimicrobial susceptibility using the CLSI recommendations for broth microdilution [7] and were interpreted following CLSI and [7] European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [8]. Minimal Inhibitory Concentration (MIC) of planktonic bacteria was obtained for each strain against clarithromycin (CHL) (Sigma-Aldrich, MA, USA) with a range of 1-256 mg/L. MAC strains were incubated for 10 days and *M. abscessus* strains were incubated for 5 days, all of them at 37ºC with 5% CO_2. After incubation, MIC values were read with the naked eye according to the CLSI/EUCAST recommendations. A positive control with bacteria without antibiotic and a negative control without microorganisms were included for each strain. This test was performed in triplicate for all strains.

Biofilm susceptibility assay. Susceptibility in biofilm was determined as proposed by Fernández-Olmos *et al.* with minor modifications [9]. Biofilm formation for all strains was reached by suspending the strains to 0.5±2 McFarland in liquid Middlebrook medium and 75 µL of each strain was placed onto a 96-well plate (ThermoFisher Scientific, MA, USA). Then, clarithromycin was added to the wells using concentrations between 0.25 and 256 mg/L and 75 µL of CHL serial dilutions to the 96-well plate to study a wide range of concentrations. The plates were incubated for 5 days for the *M. abscessus* strains and 10-15 days incubation for the MAC strains. After incubation, Biofilm Preventive Concentration (BPC) was determined by lack of biofilm formation by visual inspection using an inverted microscopy (Leica, LEITZ DM IL) and by measuring the plates in a spectrophotometer (TECAN, Switzerland) at OD_{595} nm. Positive controls with all ATCC strains were used in all the experiments. All strains were tested in triplicate. EUCAST criteria for MICs were adopted for BPCs.

RESULTS AND DISCUSSION

MICs and BPCs obtained for the *M. abscessus* strains and the MAC clinical strains are shown in Table 1. Interestingly, all but one *M. abscessus* strains showed identical BPC, while MAC isolates showed more variable concentrations, having all *M. avium* strains at the same concentration.

Biofilms are selective environments, placing demands on planktonic microbial cells. A pre-existing microbial biofilm may stimulate, inhibit, or have no effect on the adherence of a particular microbial species or type [10]. For instance, early studies of adherence relied upon having a surface covered with protein (e.g., bovine serum albumin). Without a conditioned surface a particular microorganism would not be able to adhere and form a biofilm [11]. In contrast, *M. avium* is capable of forming new biofilm thanks to its hydrophobic surface that can adhere to all types of surfaces [12].

Biofilm formation and surface adherence is an essential pathogenic factor for the *M. avium* complex because without adherence or biofilm formation cells would be washed away by any flowing force [13]. *M. avium* usually colonizes the respiratory tract of patients with chronic pulmonary disease which can evolve to an infection that is difficult to eradicate. Therefore, it is credible that biofilm formation might have a substantial effect on the maintenance of the infection. On the other hand, *M. abscessus* disease is considered a biofilm-related one, and this mycobacterium has been found forming biofilms in the lung tissue of patients with *M. abscessus* disease [14]. Moreover, many *in vitro* studies have shown that the biofilms formed by this species have an increased resistance against many antibiotics, including macrolides [15].

Table 1 **Minimum inhibitory and biofilm prevention concentration of Mycobacteria clinical strains.**

Strain	MIC (mg/L)	BPC (mg/L)	Number of dilutions between MIC and BPC
M. avium ATCC 25291	4	16	2
M. intracellulare ATCC 13950	8	8	0
M. chimaera DSM 44623	≤1	1	≥ 1
M. avium 717	≤1	16	> 4
M. avium 647	≤1	16	> 4
M. intracellulare 505	≤1	8	> 3
M. intracellulare 657	≤1	4	> 2
M. chimaera 575	≤1	1	≥ 1
M. chimaera 655	8	16	1
M. abscessus DSM 44196 rough	2	32	4
M. abscessus DSM 44196 smooth	2	32	4
M. abscessus subsp. *abscessus* 330	1	32	5
M. abscessus subsp. *abscessus* 368	4	32	3
M. abscessus subsp. *massiliense* 624	1	32	5
M. abscessus subsp. *massiliense* 611	0.25	64	8
M. abscessus subsp. *bolletii* 531	≥16	32	0

MIC, minimum inhibitory concentration; BPC, biofilm prevention concentration.

Active antibiotics against either planktonic cells or early attached cells might serve as a prevention method against biofilm formation and development. This can be confirmed with this study where the strains of all the species showed low BPCs for clarithromycin, and by the study of Carter et al, where subinhibitory concentrations of macrolides can inhibit partially the biofilm formation of several *M. avium* strains [16]. However, in our study, we looked for the concentration that inhibits completely the development of a biofilm, and this is a possible explanation of our results. Interestingly, MAC isolates showed different values, probably related to the differences detected in biofilm development among all these strains [17], differences that are not detected among *M. abscessus* strains, which are more uniform in biofilm development, as previously described [18]. The latter one is, in fact, very different from MAC, so we expected differences in the detection of BPC between both groups that were confirmed in the study. Former studies that showed the preventive value of macrolides against MAC infection in the first years of the AIDS pandemic [19] can be now explained (at least partially) for this property, because by avoiding biofilm formation we can potentially avoid the disease, and so improving the quality of life of the patients.

The main limitation of our study is the low number of tested strains. Future studies with a large sample size are needed as are studies that test other antibiotics that can be used in the treatment of nontuberculous mycobacteria. Another limitation is the lack of bovine serum in our culture medium, which can be a conditioning factor for biofilm development for mycobacteria. However, we have previously used this medium in previous studies with these species of mycobacteria with good results [17,18].

These results suggest the importance of developing an early aggressive treatment to prevent biofilm formation in this type of bacteria and open a possibility of preventive measures for these patients that potentially can change their management and outcome. However, how implementing this possibility is a matter for further research, because many issues (dosages, time, type of patients) need to be determined before introducing this type of prophylaxis in common clinical practice.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

REFERENCES

1. Daley CL. *Mycobacterium avium* Complex Disease. Schlossberg D, editor. Microbiol Spectr. 2017 Apr;5(2). doi/10.1128/microbiolspec.TNMI7-0045-2017

2. Daley CL, Iaccarino JM, Lange C, *et al*. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clinical Infectious Diseases.71(4):905-13. https://academic.oup.com/cid/article/71/4/905/5892833
3. Esteban J, Navas E. Treatment of infections caused by nontuberculous mycobacteria. Enferm Infecc Microbiol Clin (Engl Ed). 2018;36(9):586-92.
4. Leao SC, Tortoli E, Euzéby JP, *et al*. Proposal that *Mycobacterium massiliense* and *Mycobacterium bolletii* be united and reclassified as *Mycobacterium abscessus* subsp. *bolletii* comb. nov., designation of *Mycobacterium abscessus* subsp. *abscessus* subsp. nov. and emended description of *Mycobacterium abscessus*. Int J Syst Evol Microbiol. 2011;61(Pt 9):2311-3.
5. Broncano-Lavado A, Senhaji-Kacha A, Santamaría-Corral G, *et al*. Alternatives to Antibiotics against *Mycobacterium abscessus*. Antibiotics (Basel). 2022;11(10):1322.
6. Siddam AD, Zaslow SJ, Wang Y, *et al*. Characterization of Biofilm Formation by *Mycobacterium chimaera* on Medical Device Materials. Front Microbiol. 2020;11:586657.
7. CLSI. Susceptibility testing of Mycobacteria, Nocardiae, and other aerobic actinomycetes. 3rd ed. CLSI Standard M24. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
8. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0. EUCAST; 2012. http://www.eucast.org
9. Fernández-Olmos A, García-Castillo M, Maiz L, *et al*. In vitro prevention of *Pseudomonas aeruginosa* early biofilm formation with antibiotics used in cystic fibrosis patients. Int J Antimicrob Agents. 2012;40(2):173-6.
10. Falkinham JO. *Mycobacterium avium* complex: Adherence as a way of life. AIMS Microbiol. 2018;4(3):428-38.
11. Mullis SN, Falkinham JO. Adherence and biofilm formation of *Mycobacterium avium*, *Mycobacterium intracellulare* and *Mycobacterium abscessus* to household plumbing materials. J Appl Microbiol. 2013;115(3):908-14.
12. Wallace RJ, Iakhiaeva E, Williams MD, *et al*. Absence of *Mycobacterium intracellulare* and presence of *Mycobacterium chimaera* in household water and biofilm samples of patients in the United States with *Mycobacterium avium* complex respiratory disease. J Clin Microbiol. 2013;51(6):1747-52.
13. Carter G, Wu M, Drummond DC, *et al*. Characterization of biofilm formation by clinical isolates of *Mycobacterium avium*. J Med Microbiol. 2003;52(Pt 9):747-52.
14. Qvist T, Eickhardt S, Kragh KN, *et al*. Chronic pulmonary disease with *Mycobacterium abscessus* complex is a biofilm infection. Eur Respir J. 2015;46(6):1823-6.
15. Flores V da C, Siqueira FDS, Mizdal CR, *et al*. Antibiofilm effect of antimicrobials used in the therapy of mycobacteriosis. Microb Pathog. 2016;99:229-35.
16. Carter G, Young LS, Bermudez LE. A subinhibitory concentration of clarithromycin inhibits *Mycobacterium avium* biofilm formation. Antimicrob Agents Chemother. 2004; 48 (12): 4907-10.
17. Akir A, Senhaji-Kacha A, Muñoz-Egea MC, Esteban J, Aguilera-Correa JJ. Biofilm development by *Mycobacterium avium* complex clinical isolates. Effect of clarithromycin in ultrastructure. Antibiotics (Basel). 2024. 13 (3): 263..
18. Martín de Hijas NZ, García-Almeida D, Ayala G, Fernandez-Roblas R, Gadea I, Celdrán A, Gómez-Barrena E, Esteban J. Biofilm development by clinical strains of non-pigmented rapidly growing mycobacteria. Clinical Microbiology and Infection. 2009. 15 (10): 931-936.
19. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med.1996;335(6):384-91.

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Brief report

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Lucía Fraile García
Jesús Aramburu Arnuelos
Éric López González
Alba Bellés-Bellés
Alba Muñoz Santa
Elena Sánchez Báscones
Saray Mormeneo Bayo
Albert Bernet Sánchez
Iván Prats Sánchez
Alejandro Cumplido Portillo
Mercè García González

Azithromycin and moxifloxacin resistance determinants in *Mycoplasma genitalium* in Lleida, Spain

Hospital Universitari Arnau de Vilanova, Lleida, Spain. Institut de Recerca Biomèdica de Lleida (IRB-Lleida), Spain

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ABSTRACT

Introduction. *Mycoplasma genitalium* (MG) is a microorganism related to sexually transmitted infections. Antibiotic resistance of MG leads to an increase in treatment failure rates and the persistence of the infection. The aim of this study was to describe the most frequent mutations associated with azithromycin and moxifloxacin resistance in our geographical area.

Material and methods. A prospective study from May 2019 to May 2023 was performed. MG-positive samples were collected. Real-time PCRs (AllplexTM MG & AziR Assay and AllplexTM MG & MoxiR Assay, Seegene) were performed in MG positive samples to detect mutations in 23S rRNA V domain and *parC* gene.

Results. A 37.1% of samples presented resistance determinants to azithromycin and the most common mutation detected was A2059G (57.9%). Resistance to moxifloxacin was studied in 72 azithromycin-resistant samples and 36.1% showed mutations, being G248T the most prevalent (73.1%).

Conclusions. The resistance to different lines of treatment suggests the need for a targeted therapy and the performing of a test of cure afterwards.

Keywords: azithromycin; moxifloxacin; mutation; *Mycoplasma genitalium*; resistance

Determinantes de resistencia a azitromicina y moxifloxacino en *Mycoplasma genitalium* en Lleida, España

RESUMEN

Introducción. *Mycoplasma genitalium* (MG) es un microorganismo relacionado con las infecciones de transmisión sexual. La resistencia antibiótica del MG conduce a un aumento de las tasas de fracaso terapéutico y a la persistencia de la infección. El objetivo de este estudio fue describir las mutaciones más frecuentes asociadas a la resistencia a azitromicina y moxifloxacino en nuestra área geográfica.

Material y métodos. Estudio prospectivo desde mayo 2019 a mayo 2023 en el que se incluyeron todas las muestras positivas para MG (una por paciente). Se estudió la presencia de mutaciones en el dominio V del ARNr 23S y en el gen *parC* mediante PCR en tiempo real (AllplexTM MG & AziR Assay y AllplexTM MG & MoxiR Assay, Seegene).

Resultados. Un 37,1% de las muestras presentaron determinantes de resistencia a azitromicina y la mutación más común detectada fue A2059G (57,9%). La resistencia a moxifloxacino se estudió en 72 muestras resistentes a azitromicina y el 36,1% presentaron mutaciones, siendo G248T la más prevalente (73,1%).

Conclusiones. La resistencia a diferentes líneas de tratamiento sugiere la necesidad de una terapia dirigida y la realización de una prueba de curación posterior.

Palabras clave: azitromicina; moxifloxacino; mutación; *Mycoplasma genitalium*; resistencia

INTRODUCTION

Mycoplasma genitalium (MG) is a microorganism related to sexually transmitted infections (STI). The main route of transmission is direct genital-genital mucosal contact [1,2].

Correspondence:
Alba Bellés Bellés.
Sección de Microbiología y Parasitología, Hospital Universitari Arnau de Vilanova. Avenida Rovira Roure 80, 25198. Lleida, Spain.
E-mail: abelles.lleida.ics@gencat.cat

MG diagnosis has been improved in recent years. The incorporation of molecular techniques in clinical laboratories has replaced the common culture because of its low sensitivity [3,4]. However, MG is still a clinical challenge. MG is intrinsically resistant to β-lactams due to the lack of cell wall, and therefore the choice of an appropriate treatment is limited to macrolides, tetracyclines, and quinolones [5]. According to the Clinical Guidelines, azithromycin is the first line of treatment and its cure rate is approximately 85% in macrolide susceptible infections, while doxycycline has a cure rate between 30-40%. The increasing resistance rates of MG to these antibiotics has led to the use of quinolones, such as moxifloxacin, as an alternative in macrolide-resistant or complicated infections [6].

Knowledge of the main mechanisms involved in MG antibiotic resistance is essential. Azithromycin inhibits protein synthesis and its resistance is associated with mutations in the region V of the 23S rRNA gene, being the point mutations at positions 2058 and 2059 the most frequent ones [7]. Azithromycin-resistant MG (Azi-R-MG) has been reported worldwide in the last years [2,5,8-11]. On the other hand, mutations in the *parC* and/or *gyrA* are responsible for moxifloxacin-resistant MG (Moxi-R-MG) [12]. Novel technologies to detect these mutations which include real-time PCR are excellent options to characterize these mechanisms when sequencing is not available [11]. The evaluation of acquired moxifloxacin resistance has been conducted in several studies, but the sample size evaluated is still not sufficient [1-3,7].

The aim of this study was to describe the prevalence of MG mutations associated with azithromycin and moxifloxacin resistance in the sanitary region of Lleida, Spain.

METHODS

A prospective study from May 2019 to May 2023 was performed at Hospital Universitari Arnau de Vilanova (Lleida, Spain), a referral tertiary hospital in northeast Spain covering an area of approximately 340,000 inhabitants.

MG-positive samples from patients with clinical suspicion of a STI, sexual partner diagnosed with a STI or as a screening test for pregnant women with less than 25 years old were collected. The specimens included urethral swabs, first-void urines, endocervical swabs and rectal swabs. Only one positive sample per patient was evaluated.

DNA was extracted using EZ1 or QIASymphony equipment (QIAGEN), and real-time PCR screening was performed on the CFX96 qPCR instrument (Bio-Rad) using the Allplex™ STI Essential Assay (Seegene) for the detection of MG and other pathogens causing STI (*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV), *Mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum*).

A multiplex qPCR assay (Allplex™ MG & AziR Assay, Seegene) that detects MG and the most frequent mutations associated with azithromycin resistance (A2058G, A2058T, A2058C, A2059G, A2059T, A2059C) was performed in MG-positive samples.

Samples from patients already studied (less than six weeks), asymptomatic and/or with different kind of specimens the same day were excluded from resistance study.

Azi-R-MG samples were also tested for moxifloxacin resistance determinants since December 2019. Thereby, a multiplex qPCR (Allplex™ MG & MoxiR Assay, Seegene), that detects MG and six frequent mutations in *parC* gene (A247C, G248A, G248T, G259A, G259C, G259T) was performed.

The medical records of Azi-R-MG patients were reviewed by collecting demographic data, antibiotic treatment prescribed, the ongoing coinfections with other pathogens causing STI (CT, NG, TV) and the performance and result of test of cure (TOC), described as a second PCR performed for the detection of MG at least 4 weeks after the end of the treatment.

RESULTS

A total of 256 MG-positive samples were analyzed during the period of the study. MG was detected in 178 samples from men (69.5%) and 78 from women (30.5%). The median age of MG-positive patients was 27 years (range 17-69). Demographic and clinical characteristics of patients are summarized in Table 1.

The qPCR assay that detects the most frequent mutations associated with Azi-R-MG was performed on the 256 samples. Determinants of azithromycin resistance were detected in 95 samples (37.1%, 95/256) and 75.8% of them (72/95) were men. The most frequently detected mutation was A2059G (55/95), followed by A2058G (22/95), A2058T (10/95), A2059C (6/95) and A2058C (2/95).

Regarding moxifloxacin, the qPCR assay that detects quinolones resistance determinants was performed on 72 Azi-R-MG samples since December 2019. Mutations in *parC* were found in 26 samples (26/72, 36.1%). The most frequently detected mutation was G248T (19/26), followed by G248A (4/26), G259A (2/26) and G259T (1/26). No A247C or G259C mutations were detected.

Seventy two of the 95 Azi-R-MG samples were detected in men and 38 (52.8%) of them were men who had sex with men (MSM). A mutation related to Moxi-R-MG was detected in seven of these 38 MSM (18.4%).

Data about previous antibiotic treatment was available in 89 patients, 45 of whom (45/89, 50.6%) were treated with azithromycin before this episode.

The 7.4% (7/95) of Azi-R-MG cases presented co-infections with other pathogens causing STI: CT (n=6) and TV (n=1). The 22.1% (21/95) of patients with Azi-R-MG were HIV-positive (20 men and 1 woman). HIV-positive men were all MSM.

Data on TOC performance was available in 70 of the 95 Azi-R-MG patients. The 87.1% (61/70) showed a negative TOC (no detection of MG). In the case of the specimens with a Moxi-R-MG, data was available in 21 cases and 15 patients had a negative TOC (15/21, 71.4%). G248T mutation in *parC* gene was the most common mutation (n=4) in individuals with a positive TOC.

Tabla 1 **Demographic and clinical characteristics of patients with *Mycoplasma genitalium* detection (Lleida, 2019-2023).**

Total MG positive samples (n=256)			Men		Women	
			178	69.5%	78	30.5%
AZI-R-MG	95/256	37.1%	72/178	40.4%	23/78	29.5%
MSM			38/72	52.8%		
HIV+	21/95	22.1%	20		1	
First void urine	50/95	52.6%	46		4	
Urethral swab	10/95	10.5%	10		0	
Rectal swab	16/95	16.8%	16		0	
Endocervical swab	19/95	20.0%	0		19	
parC mutations test performed (n=72)			51	70.8%	21	29.2%
MOXI-R-MG	26/72	36.1%	13/51	25.5%	13/21	61.9%

AZI-R-MG (Azithromycin-resistant-MG), MOXI-R-MG (Moxifloxacin-resistant-MG).

DISCUSSION

In this study we described the mutations in MG that confer resistance to azithromycin or moxifloxacin. It is a continuation of a previous one performed between 2019-2021 in which Muñoz-Santa *et al* evaluated the prevalence of MG and mutations related to azithromycin resistance in our area [5]. The main mutation detected in Azi-R-MG in the present study has been A2059G (55/95, 57.9%), which was the most frequent in the fore-mentioned report (55.6%). Our results are similar to those performed in other Spanish areas: a study performed in Tenerife (Canary Islands, Spain) found that 17 out of 28 samples have the A2059G mutation [11], and in a report from the south of Spain, the same mutation was described in the 50% of Azi-R-MG samples [9].

The increasing azithromycin resistance in different geographical areas points us towards the study of moxifloxacin resistance, the second line of treatment according to Clinical Guidelines [6]. In our study, moxifloxacin resistance was assessed in samples that were already resistant to azithromycin. The main *parC* mutation detected was G248T (19/26), which agrees with previously reports [3,7,10]. In our study, we only evaluated the *parC* gene, although some studies reported that resistance to moxifloxacin is also due to mutations in *gyrA* gene [11,14,15].

We reported 9/70 (12.9%) MG cases treated with azithromycin with treatment failure. A2059G was the mutation detected in 7 of these patients. It is unclear if there is a connection, or it is just because it is the most frequent mutation detected in different studies [3,5,7]. That is not the case with the *parC* G248T mutation, which is the main mutation described in association with moxifloxacin treatment failure [10,14]. This mutation was found in 4 (66.7%) of our 6 Moxi-R-MG samples with a positive TOC. However, more studies are needed to conclude that the mutations detected are responsible for treatment failure.

The presence of co-infections with others pathogens causing STI means the treatment prescribed was not restricted to MG. Five patients with co-infections (5/7, 71.4%) were negative for the TOC performed. The resolution of the infection could be explained by the involvement of different antibiotic treatments, but it would be necessary to consider that we have a limited number of samples with these characteristics in order to reach conclusions.

A previous azithromycin treatment for an STI or respiratory infection could explain the high resistance associated with azithromycin treatment [7,9,15]. Upon collecting data from the clinical story of patients with an Azi-R-MG infection, we observed that approximately half of the patients (45/89) had previously received treatment with this antibiotic.

Several studies demonstrate a high prevalence of resistant MG infection in MSM [5,7,9]. As it was previously described, we found that 52.8% of men with an Azi-R-MG were MSM. The high bacterial STI burden and frequent exposure to macrolide treatment may account for the high prevalence of macrolide-resistant MG among MSM [2].

It is important to keep on evaluating patients with a MG infection and its resistance mechanisms. The main conclusion reported in our study is that the concerning resistance to azithromycin and the increasing resistance to the second line treatment (moxifloxacin), correlated with treatment failure and the persistence of MG infection. As we previously mentioned, we did not evaluate the *gyrA* gene by sequencing for moxifloxacin resistance, unlike other studies [11, 14]. More studies with a larger number of samples to relate combinations of mutations responsible for azithromycin and/or moxifloxacin treatment failure are needed.

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None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest

REFERENCES

1. Piñeiro L, Idigoras P, De La Caba I, et al. Tratamiento antibiótico dirigido en infecciones por *Mycoplasma genitalium*: análisis de mutaciones asociadas con resistencia a macrólidos y fluoroquinolonas. Enfermedades Infecc Microbiol Clínica. 2019 Jun;37(6):394–7. https://doi.org/10.1016/j.eimc.2018.10.003
2. Sandri A, Carelli M, Visentin A, et al. *Mycoplasma genitalium* antibiotic resistance-associated mutations in genital and extragenital samples from men-who-have-sex-with-men attending a STI clinic in Verona, Italy. Front Cell Infect Microbiol. 2023 Mar 31;13:1155451. https://doi.org/10.3389/fcimb.2023.1155451
3. Piñeiro L, Idigoras P, Arrastia M, et al. Increases in the Macrolide Resistance of *Mycoplasma genitalium* and the Emergence of the A2058T Mutation in the 23S rRNA Gene: Clonal Spread? Antibiotics. 2022 Oct 27;11(11):1492. https://doi.org/10.3390/antibiotics11111492
4. Meseguer-Peinado MA, Acosta-Boga B, Matas-Andreu L, et al. Diagnóstico microbiológico de las infecciones por *Mycoplasma*. Enfermedades Infecc Microbiol Clínica. 2012 Oct;30(8):500–4. https://doi.org/10.1016/j.eimc.2011.10.020
5. Muñoz Santa A, Aramburu Arnuelos J, Bernet Sánchez A, et al. *Mycoplasma genitalium*: Analysis of mutations associated with macrolide resistance in Lleida, Spain. Enfermedades Infecc Microbiol Clínica. 2022 Apr;40(4):209–10. https://doi.org/10.1016/j.eimc.2021.02.004
6. Jensen JS, Cusini M, Gomberg M, et al. 2021 European guideline on the management of *Mycoplasma genitalium* infections. J Eur Acad Dermatol Venereol. 2022 May;36(5):641–50. https://doi.org/10.1111/jdv.17972
7. Barberá MJ, Fernández-Huerta M, Jensen JS, et al. *Mycoplasma genitalium* Macrolide and Fluoroquinolone Resistance: Prevalence and Risk Factors Among a 2013–2014 Cohort of Patients in Barcelona, Spain. Sex Transm Dis. 2017 Aug;44(8):457–62. https://doi.org/10.1097/olq.0000000000000631
8. Asenjo A, Kusters JG, Severs TT, et al. *Mycoplasma genitalium* in Spain: prevalence of genital infection and frequency of resistance to macrolides. Enfermedades Infecc Microbiol Clínica. 2018 Mar;36(3):169–71. https://doi.org/10.1016/j.eimc.2017.01.006
9. de Salazar A, Barrientos-Durán A, Espadafor B, et al. Macrolide and fluoroquinolone resistance of *Mycoplasma genitalium* in southern Spain, 2018–2019. Sex Transm Infect. 2021 Feb;97(1):8–10. https://doi.org/10.1136/sextrans-2019-054386
10. Murray GL, Bodiyabadu K, Vodstrcil LA, et al. parC Variants in *Mycoplasma genitalium*: Trends over Time and Association with Moxifloxacin Failure. Antimicrob Agents Chemother. 2022 May 17;66(5):e00278-22. https://doi.org/10.1128/aac.00278-22
11. Mateo León C, García Martínez De Artola D, Pino-Calm B. High macrolides and fluoroquinolones resistance rate in *Mycoplasma genitalium* in southern Tenerife. Rev Esp Quimioter. 2023 Jul 7;36(4):416–20. https://doi.org/10.37201/req/014.2023
12. Raj Js, Rawre J, Dhawan N, et al. *Mycoplasma genitalium* : A new superbug. Indian J Sex Transm Dis AIDS. 2022;43(1):1. https://doi.org/10.4103/ijstd.ijstd_103_20
13. Lucena Nemirosky J, Espelt R, López Grado E, et al. Macrolide resistance in *Mycoplasma genitalium* in Catalonia, Spain: a 1 year prospective study. J Antimicrob Chemother. 2021 Sep 15;76(10):2702–7. https://doi.org/10.1093/jac/dkab224
14. Murray GL, Plummer EL, Bodiyabadu K, et al. *gyrA* Mutations in *Mycoplasma genitalium* and Their Contribution to Moxifloxacin Failure: Time for the Next Generation of Resistance-Guided Therapy. Clin Infect Dis. 2023 Jun 16;76(12):2187–95. https://doi.org/10.1093/cid/ciad057
15. Machalek DA, Tao Y, Shilling H, et al. Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium*: a systematic review and meta-analysis. Lancet Infect Dis. 2020 Nov;20(11):1302–14. https://doi.org/10.1016/S1473-3099(20)30154-7

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Carta al Director

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Telmo Fernandez de Casadevante[1]
Xabier Camino[2]
Ainhoa Arteche[1]
Ana Alonso[3]
Paul Martinage[3]

Endocarditis infecciosa por *Listeria monocytogenes*: Caso tratado sin intervención quirúrgica con adecuada evolución clínica

[1]Servicio de Anestesiología, Reanimación y Terapéutica del dolor, Hospital Universitario Donostia, España
[2]Unidad de Enfermedades Infecciosas. Hospital Universitario Donostia, España
[3]Servicio de Medicina Interna. Hospital Universitario Donostia, España

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Presentamos un caso de endocarditis infecciosa aguda producida por *Listeria monocytogenes* y resuelta con tratamiento médico exclusivamente.

Caso: varón de 71 años que ingresa por sensación distérmica y malestar general de días de evolución, presentando un cuadro parecido sin etiología establecida 3 meses antes. Antecedentes personales: hipertensión arterial, diabetes mellitus tipo 2, vértigo posicional benigno, episodio de fibrilación auricular revertido en tratamiento anticoagulante, y una estenosis aórtica severa y dilatación de aorta ascendente. Intervenido hace 2 años con colocación de tubo valvulado aórtico por insuficiencia aórtica severa y dilatación de raíz. La exploración física no muestra hallazgos significativos. No presenta alteraciones analíticas de interés en el momento del ingreso. En los hemocultivos realizados presenta un crecimiento de *L. monocytogenes* en 4/4. Se realiza un ecocardiograma transtorácico que resultó no concluyente por mala ventana. En el ecocardiograma transesofágico se aprecian varias imágenes móviles en los velos del ventrículo izquierdo y a nivel superior de los senos de Valsalva compatibles con vegetaciones. Se observa también un engrosamiento heterogéneo a nivel perianular compatible con un absceso periprotésico. Se realiza un TAC-TA, que muestra una colección hipodensa en torno a la aorta ascendente, y lo mismo a nivel de la válvula aórtica, además de imagen compatible con infarto esplénico. Se inicia tratamiento con ampicilina 3g/6h y gentamicina 80mg/8h el mismo día del ingreso. El estudio es completado con una RMN craneal, en la que se observa una lesión compatible con cerebritis con afectación leptomeníngea vs embolia. El PET-TAC añade la presencia de unos ganglios hilio-mediastínicos bilaterales hipermetabólicos de carácter reactivo al hipermetabolismo de la válvula aórtica y aorta ascendente. Dada la morbilidad del paciente se realiza un tratamiento no quirúrgico, modificando la gentamicina por cotrimoxazol 1600/320mg/8h debido a un descenso del filtrado glomerular, manteniendo la ampicilina durante 8 semanas desde el diagnóstico. El paciente presenta una mejoría clínica, con hemocultivos de control realizados a los 7 días post-antibiótico negativos. El paciente realiza seguimiento en consulta durante 18 meses tras finalizar el tratamiento encontrándose asintomático y con hemocultivos de control repetidamente negativos.

A pesar de los avances médicos, la endocarditis infecciosa (EI) conserva una elevada morbimortalidad (0,87 muertes por cada 100.000 personas de la población) [1]. Además, sigue siendo un reto diagnóstico debido al amplio abanico de manifestaciones clínicas con las que puede presentarse, ello dependiendo de; edad del paciente [2], microorganismo causante, y presencia de antecedentes previos como hepatopatía, insuficiencia renal, valvulopatías, et al. Todo ello hace que se requiera de colaboración multidisciplinaria para su manejo [3].

A esto se le añade que el microorganismo causante es una *L. monocytogenes*, bacilo grampositivo aeróbico, causante de sepsis, meningoencefalitis, y una amplia variedad de infecciones (artritis, osteomielitis, peritonitis, hepatitis, colecistitis y endocarditis) todas ellas con una gran morbimortalidad [1,4,5]. Es de destacar que el causante del cuadro representa el 0,3% de todas las EI [1]. Los pacientes afectados por EI por dicho microorganismo resultan ser habitualmente de edad avanzada, dándose la mayoría en varones, y más aun en aquellos con válvulas protésicas, a pesar de que la L. monocytogenes afecte más frecuentemente a mujeres. Se ha descrito una mayor tendencia a la afectación de pacientes diabéticos y con válvula protésica, probablemente por la tendencia de esta bacteria a afectar a pacientes inmunodeprimidos y con factores predisponentes [6].

El pronóstico empeora más aún si al cuadro de EI se le asocian complicaciones neurológicas [1,5]. Por ello, cabe destacar la exploración neurológica normal que presentó el paciente

Correspondencia:
Telmo Fernandez de Casadevante
H. U. Donostia
Begiristain Doktorea Pasealekua, s/n, 20014 Donostia, Gipuzkoa
E-mail: telmofdec@gmail.com

en todo momento (salvo los vértigos), a pesar del hallazgo de posible cerebritis en la RMN craneal.

Finalmente, el tratamiento incluye antibióticos y cirugía, que, según las últimas guías de práctica clínica, debería haberse realizado en nuestro caso por las imágenes sugestivas de abscesos cardiovasculares [1,4], que según las últimas guías aumentan el riesgo de embolismos sépticos extracardíacos, empeorando el pronóstico. Se ha visto que el tratamiento médico conservador en estos casos implica un peor pronóstico global [4], a pesar de que nuestro caso evolucionase correctamente.

Según los casos revisados, más de un tercio de los pacientes con EI sobre válvulas protésicas tratadas médicamente tienen una mala evolución [6,7]. Dicho dato, comparándolo con el 9,1% de mortalidad que tienen los EI sobre válvulas protésicas tratadas médico-quirúrgicamente [7], resulta contradictorio con la evolución observada en el caso expuesto.

En resumen, el cuadro de EI por *L. monocytogenes* resulta poco común y de gran morbi-mortalidad, mayor en los pacientes que sólo reciben tratamiento médico [7]. A pesar de ello, el caso presentado tuvo buena evolución.

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CONFLICTO DE INTERESES

Los autores declaran que no presentan conflictos de intereses en relación con el presente artículo.

BIBLIOGRAFÍA

1. Fernández-Hidalgo N, Tornos Mas P. Epidemiología de la endocarditis infecciosa en España en los últimos 20 años. Rev Esp Cardiol. 2013; 66(9):728–33. https://doi.org/10.1016/j.recesp.2013.05.00
2. Sedano R, Fica A, Guiñez D, Braun S, Porte L, Dabanch J, et al. Infecciones por Listeria monocytogenes, una experiencia de dos décadas: A two decade experience. Rev Chilena Infectol. 2013; 30(4):417–25. http://dx.doi.org/10.4067/S0716-10182013000400011
3. Marín A, Lustig N, Cruz R, Córdova S. Endocarditis infecciosa por Listeria monocytogenes: revisión de la literatura a partir de un caso clínico. Rev Chilena Infectol. 2013; 30(4):436–40. http://dx.doi.org/10.4067/S0716-10182013000400013
4. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M,et al. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J. 2023 Oct 14;44(39):3948-4042. https://doi.org/10.1093/eurheartj/ehad193
5. García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: Risk factors, outcome, and impact of cardiac surgery: A multicenter observational study. Circulation. 2013;127(23):2272–84. https://doi.org/10.1161/CIRCULATIONAHA.112.000813
6. García-Granja PE, López J, Vilacosta I, Olmos C, Sarriá C, San Román JA. Endocarditis infecciosa por Listeria monocytogenes: a propósito de 4 casos. Rev Esp Cardiol. 2016; 69(7):700–https://doi.org/10.1016/j.recesp.2016.03.010
7. Fernández Guerrero ML, Rivas P, Rábago R, Núñez A, de Górgolas M, Martinell J. Prosthetic valve endocarditis due to Listeria monocytogenes. Int J Infect Dis. 2004; 8(2):97–102. https://doi.org/10.1016/j.ijid.2003.06.002

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Letter to the Editor

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Miguel Camara-Rodriguez[1]
Francisco Jover-Diaz[1,2]
Elisabet Delgado-Sánchez[2]
Ana Infante-Urríos[3]
Jorge Peris-García[1,2]

Dalbavancin as long-term treatment in *Corynebacterium striatum* Infections: a literature review

[1]Departamento de Medicina Clínica. Universidad Miguel Hernández. Elche, Alicante. Spain.
[2]Unidad de Enfermedades Infecciosas. Hospital Clínico Universitario San Juan. Alicante. Spain.
[3]Sección de Microbiología Clínica. Hospital Clínico Universitario San Juan. Alicante. Spain.

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Sir,

Corynebacterium striatum is a facultative anaerobic gram-positive bacillus. Usually, it has been considered an opportunistic pathogen that colonizes skin and mucous membranes. Recent years have seen the emergence of C. striatum as a novel pathogen, particularly in those with compromised immune systems or those experiencing nosocomial outbreaks. Biofilms are a common occurrence in patients undergoing surgery or those who have received a prosthetic device, as evidenced by the presence of biofilms [1]. Its adherence to prosthetic surfaces (both hydrophobic and hydrophilic) has been attributed to the binding of fibrinogen. Recent reports of systemic infections, such as endocarditis, meningitis, osteomyelitis, and respiratory infections, as well as notable pathogens in bone and joint infections (septic arthritis), have been published [2-3]

Many laboratories do not routinely identify Corynebacterium species because they are frequently isolated as contaminants. Then their identification in culture is challenging for clinicians. New diagnostic identification technologies in clinical microbiology laboratories, such as MALDI-TOF MS, have been reported to be more accurate compared to conventional biochemical methods [2].

C. striatum exhibits limited susceptibility compared to other *Corynebacterium* species. Resistance to penicillins, cephalosporins, carbapenems, clindamycin, and fluoroquinolones is common. Susceptibility to vancomycin and linezolid is frequently found in clinical samples [3]. Then, these are the most appropriate antibiotics for *C. striatum* infections. However, both vancomycin and linezolid have significant toxicity in elderly patients. Also, vancomycin requires drug monitoring levels Therefore, the new unauthorized use of alternative medications is necessary.

Correspondence:
Jover Diaz Francisco.
Unidad de Enfermedades Infecciosas. Hospital Clínico Universitario San Juan. Alicante. Spain.
E-mail: fjover@umh.es

Although *C. striatum* is frequently susceptible to daptomycin, some could show daptomycin resistance or clinical failure. Chauvelot *et al.* [4] described three patients treated with daptomycin who experienced treatment failure.

Dalbavancin is a novel semisynthetic lipoglycopeptide with significant potency against a wide spectrum of Gram-positive pathogens. Its long half-life enables at least weekly administration. Rolston *et al.* [5] compared dalbavancin in vitro activity with that of vancomycin, daptomycin, linezolid, trimethoprim/sulfamethoxazole and levofloxacin against Gram-positive organisms isolated from cancer patients. Dalbavancin exhibited a more potent activity than vancomycin and daptomycin against most staphylococcal isolates, *Bacillus* spp., *Micrococcus* spp. and various streptococci. All 23 *Corynebacterium* spp. isolates were inhibited by ⩽0.03 mg/L of dalbavancin (range 0.008–0.03 mg/L). The MICs for vancomycin, daptomycin, trimethoprim/sulfamethoxazole and linezolid of these isolated were several times higher than dalbavancin.

We here present an elderly woman with an early prosthetic hip *C. striatum* infection successfully treated with debridement, antibiotics, and implant retention (DAIR), followed by long-term dalbavancin therapy.

A 91-year-old still-active female with a history of high blood pressure, moderate aortic stenosis, hypothyroidism, and severe pulmonary hypertension underwent a partially cemented left-sided total hip arthroplasty due to a sub-capital hip fracture in March 2023. Four weeks later, she consulted due to wound leakage to her general practitioner. She was immediately transferred to the orthopaedic surgery emergency department. On presentation, she was febrile at 38.5°C. The patient's left lower extremity was edematous, and examination of the left hip revealed minimal erythema, tenderness to palpation, and a decreased range of motion secondary to pain. She underwent a regimen of debridement, antibiotics, irrigation, and retention of the prosthesis (DAIR) in the operating room 24 hours after admission. Extensive necrotic tissue and pus were noted during the surgery. Thorough excision of the

Table 1 ***C. striatum*** **infections treated with dalbavancin**

Author [reference], year	Number of cases	Type of infection	Corynebacterium species	Previous therapies	Dalbavancin indication	Dalbavancin dose regimen	Adverse effects	Outcome
Molina-Collada [6], 2017	n=1	Septic native knee arthritis	*C. striatum*	Linezolid Teicoplanin	Failure (n=1)	1500 mg (one dose)	None (n=1)	Cure (n=1)
Navarro-Jiménez [7], 2022	n=7	Diabetic foot osteomyelitis	*C. striatum*	Cotrimoxazole, tedizolid, ciprofloxacin, linezolid, amoxicillin-clavulanate, clindamycin	Failure (n=3) Side effects (n=3) Failure and Side effects (n=1)	1500 mg (one dose) to 1500 mg weekly for 5 weeks	None (n=5) Nausea (n=1)	Cure (n=6) Failure (n=1)
Mansoor [8], 2023	n=6	LVAD	*C. striatum*	Vancomycin, tedizolid, daptomycin, levofloxacin, omadacycline	Convenience (n=5) Side effects (n=1)	1500 mg every two weeks	None (n=6)	Cure (n=3) Heart transplantation (n=1) Failure (n=1) LVAD thrombosis (n=1)
Soderqüist [9],2023	n=1	PJI	*C. striatum*	Vancomycin, linezolid, daptomycin	Side effects (n=1)	1500 mg every week for 12 weeks	None (n=1)	Cure (n=1)
Camara [present case], 2023	n=1	PJI	*C. striatum*	vancomycin	Convenience (n=1)	1000 mg (load dose) and 500 mg weekly for 6 weeks.	None (n=1)	Cure (n=1)

LVAD: Left Ventricular Assist Device; PJI: Periprosthetic joint infection.

necrotic tissue, rinsing and lavage, and exchange of the femoral head were performed, and six tissue biopsies were taken for culture. Empirical treatment with intravenous meropenem and vancomycin was instituted. In the biopsies, the growth of *C. striatum* was denoted. The antibiogram revealed resistance to penicillin, clindamycin, daptomycin and quinolones while being sensitive to vancomycin, linezolid, and rifampicin. Meropenem was discontinued, but a seven-day course of vancomycin was continued. Thereafter, a loading dose (1,000 mg) of dalbavancin was administered, followed by 500 mg weekly for 5 more weeks. The patient was monitored, and normal serum creatinine and GFR (83 mL/min/1.73 m^2) were noted. The local status of the soft tissue improved very slowly, with the resolution of inflammation of the hip and thigh after dalbavancin was stopped. At the follow-up in October 2023, the patient's CRP value was 0.40 mg/dL, and her extremity's inflammation had significantly declined. Her functional status was good, and she used only one walking aid outdoors.

We reviewed the scarce English literature published regarding the use of this novel antibiotic in *C. striatum* infections through a PubMed database search using the descriptors "dalbavancin", "Corynebacterium", and "infection". The main characteristics of the sixteen patients with *C. striatum* infections treated with dalbavancin are summarized in Table 1. We found four case series describing sixteen cases treated with dalbavancin (including the present case). Except for the first case reported in 2017, the remaining cases (15/16) have been recently reported between the years 2022 and 2023. Cases can be grouped into three indications: prosthetic or native osteoarticular infection (n=3), diabetic foot infections (n=7) and left ventricular assist device (LVAD; n=6). All cases received dalbavancin as at least second-line or rescue treatment (mean of 2 prior treatments). Vancomycin or linezolid were initially prescribed as treatments.

Dalbavancin indications were previous treatment failure (n=5), antibiotic side effects (n=6) and convenience (n=6). This latter indication may arouse the greatest interest in its use, as it represents an early use based on a weekly dose of the drug, as it was in our case. Dalbavancin simplifies intravenous treatment, allowing earlier patient discharge and avoiding daily venous access use, as well as vancomycin renal toxicity. In addition, linezolid poses a risk of hematological and nervous system toxicity in such an elderly patient. In contrast, dalbavancin's tolerability in the sixteen reviewed cases was excellent. No discontinuation due to adverse effects of the drug was reported.

It is noteworthy that many patients treated for diabetic foot infections (6/7) and osteoarticular infections (3/3) were cured. On the contrary, efficacy in endovascular infections was lower (3/6). These are chronic infections in which the existence of biofilm makes eradication of the microorganism difficult.

Dalbavancin has been approved for the treatment of bacterial skin and soft tissue infections as a two-dose regimen

(1,000 mg as a loading dose and one additional dose of 500 mg after 1 week) or as a single dose of 1,500 mg intravenously. However, it has also been considered for the treatment of conditions requiring prolonged antibiotic courses, such as joint and bone infections and cardiovascular infections, with or without devices. The optimal dosing and dosing interval of dalbavancin in these clinical scenarios remain to be defined. Dunne *et al.* [10] found that the steady state was reached without accumulation for 8 weeks in an extended-dosing study with 500 mg weekly administrations of dalbavancin following loading doses. However, after four weeks of use, therapeutic drug monitoring is highly recommended. Recently, some international dosing recommendations have been published based on expert panel proposals that accommodate different healthcare settings and resource availability and centre around the length of treatment duration, including up to or exceeding 6 weeks [11]. To achieve adequate dalbavancin concentrations for up to 6 weeks, 3,000 mg of dalbavancin should be given over 4 weeks for the agreed-upon complex infections requiring > 2 weeks of treatment. Therapeutic drug monitoring (TDM) is advised for longer treatment durations and in cases of renal failure.

To conclude, long-term (up to 12 weeks) dalbavancin therapy could be a successful and safe alternative for *C. striatum* infections, especially in cases of soft tissue infections such as diabetic foot and osteoarticular infections. Its role in endovascular *C. striatum* infections remains to be defined with prospective studies. Although the optimal dosing and interval of dalbavancin for extended treatment of bone and joint infections remain to be defined, therapeutic drug monitoring could help guide it.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

REFERENCES

1. Fernández-Esgueva M, et al. Infección de prótesis de rodilla por Corynebacterium striatum. Enferm Infecc Microbiol Clin.2019;37:480–491. doi: 10.1016/j.eimc.2018.05.007.
2. Streifel AC, Varley CD, Ham Y, Sikka MK, Lewis JS 2nd. The challenge of antibiotic selection in prosthetic joint infections due to Corynebacterium striatum: a case report. BMC Infect Dis. 2022;22:290. doi: 10.1186/s12879-022-07270-0.
3. Hernandez NM, Buchanan MW, Cullen MM, Crook BS, Bolognesi MP, Seidelman J, et al. Corynebacterium total hip and knee arthroplasty prosthetic joint infections. Arthroplasty Today. 2020;6:163–8. doi: 10.1016/j.artd.2020.03.008
4. Chauvelot P, Ferry T, Tafani V, Diot A, Tasse J, Conrad A, et al. Bone and joint infection involving Corynebacterium spp.: From clinical features to pathophysiological pathways. Frontiers in Medicine. 2021;7. doi: 10.3389/fmed.2020.539501.
5. Rolston KV, Wang W, Nesher L, Shelburne SA, Prince RA. In vitro activity of dalbavancin and five comparator agents against common and uncommon Gram-positive organisms isolated from cancer patients. J Antibiot (Tokyo). 2016; 69:381-7. doi: 10.1038/ja.2015.120.
6. Molina Collada J, Rico Nieto A, Díaz de Bustamante Ussia M, Balsa Criado A. Septic arthritis in a native knee due to Corynebacterium striatum. Reumatol Clin (Engl Ed). 2018;14:301-302. doi: 10.1016/j.reuma.2017.01.013.
7. Navarro-Jiménez G, Fuentes-Santos C, Moreno-Núñez L, Alfayate-García J, Campelo-Gutierrez C, Sanz-Márquez S et al. Experience in the use of dalbavancin in diabetic foot infection. Enferm Infecc Microbiol Clin (Engl Ed). 2021 Jan 12:S0213-005X(20)30416-X. doi: 10.1016/j.eimc.2020.11.013.
8. Mansoor AE, Krekel T, Cabrera NL. Experience with dalbavancin for long-term antimicrobial suppression of left ventricular assist device infections. Transpl Infect Dis. 2023;25:e14068. doi: 10.1111/tid.14068.
9. Söderquist B, Henningsson T, Stegger M. Corynebacterium striatum prosthetic joint infection successfully treated with long-term dalbavancin. Microorganisms. 2023;11:550. doi: 10.3390/microorganisms11030550.
10. Dunne MW, Puttagunta S, Sprenger CR, Rubino C, Van Wart S, Baldassarre J. Extended-duration dosing, and distribution of dalbavancin into bone and articular tissue. Antimicrob Agents Chemother. 2015 Apr;59(4):1849-55. doi: 10.1128/AAC.04550-14.
11. Senneville E, Cuervo G, Gregoire M, Hidalgo-Tenorio C, Jehl F, Miro JM et al. Expert Opinion on Dose Regimen and Therapeutic Drug Monitoring for Long-Term Use of Dalbavancin: Expert Review Panel. Int J Antimicrob Agents. 2023; 62: 106960. doi: 10.1016/j.ijantimicag.2023.106960.

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Carta al Director

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Belén Cuadrado García[1]
Ana Madueño Alonso[1]
Ana Martín Bermúdez[1]
Lucía Romero-Acevedo[2]
Paula Pérez Orán[3]
María Lecuona Fernández[1]

Diagnóstico rápido de un caso de meningitis posquirúrgica con BioFire® Joint Infection Panel

[1]Servicio de Microbiología y Control de la Infección. Complejo Hospitalario Universitario de Canarias. San Cristóbal de La Laguna, España.
[2]Servicio de Medicina Interna. Complejo Hospitalario Universitario de Canarias. San Cristóbal de La Laguna, España.
[3]Servicio de Neurocirugía. Complejo Hospitalario Universitario de Canarias. San Cristóbal de La Laguna, España.

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Los paneles sindrómicos de PCR multiplex han permitido la identificación rápida y precisa de diversos patógenos, apoyando el diagnóstico de infecciones respiratorias, gastrointestinales, del sistema nervioso central, articulares y en bacteriemias.

El BioFire® Joint Infection Panel (BJIP) (BioMérieux), es un ensayo multiplex para la detección de 15 bacterias grampositivas, 14 bacterias gramnegativas, 1 levadura y 8 genes de resistencia antimicrobiana en muestras de individuos con sospecha de infección articular, al estar estos organismos asociados a infecciones óseas y articulares [1]. Sólo las muestras de líquido sinovial están validadas para su uso con este panel y no hay evidencia respecto a la utilidad diagnóstica de su aplicación en otras infecciones. Disponer de estos paneles para muestras estériles como el líquido cefalorraquídeo (LCR), permitiría adelantar el diagnóstico etiológico en casos de sospecha de meningitis posquirúrgica, al abarcar la detección de patógenos no habituales en meningitis bacteriana adquirida en la comunidad [2,3].

Se presenta el caso de un varón de 82 años con antecedentes personales de estenosis aórtica que acudió al servicio de urgencias por presentar trastorno en la marcha y dificultad en el lenguaje de 2-3 días de evolución. El paciente había sido intervenido 11 días antes por tumoración temporal derecha mediante biopsia ampliada de la lesión cerebral ocupante, y dado de alta con dexametasona.

A su llegada a urgencias, el paciente estaba consciente y orientado, con Glasgow de 15, pupilas isocóricas y normorreactivas, sin nistagmus y pares craneales conservados. Presentaba paresia de 4/5 en miembro inferior derecho, pero flexoextensión de rodilla y rotación de cadera, además de rotación de tobillo de 3/5. Se le solicitó un TAC craneal donde se informó encefalomalacia temporal derecha con edema adyacente y engrosamiento cortical frontal derecho, sugestivo de infiltración tumoral, así como desplazamiento de 6 mm de estructuras cerebrales respecto a la línea media en relación con herniación subfacial, sin aparentes cambios respecto al TAC previo. Se pautó dexametasona 4mg/8h y se indicó observación.

Ante la elevación de la proteína C reactiva con leucocitosis, se inició antibioterapia con meropenem 2g/8h. El paciente mantenía buen nivel de conciencia, pero se encontraba mutista. Debido a la sospecha de meningitis posquirúrgica, se practicó punción lumbar obteniendo líquido turbio amarillento y se añadió al tratamiento vancomicina 1g/12h. Los resultados de la bioquímica del LCR fueron: 195 hematíes/mm^3; 2679 leucocitos/mm^3 (96% segmentados); glucosa 40 mg/dL; proteínas 156,1 mg/dL. En la tinción de gram del LCR se observaron polimorfonucleares y bacilos gramnegativos, ante lo cual se realizó el BJIP detectando *Klebsiella aerogenes,* pero ninguno de los genes de resistencia incluidos en el panel. Debido a estos resultados se suspendió la vancomicina.

El LCR se sembró en agar sangre, chocolate y caldo tioglicolato. Tras 72h de incubación no se observó crecimiento en los medios de cultivo sólidos, pero sí en el caldo, por lo que se sembró en agar sangre. A las 24h de incubación, se recuperó el bacilo gramnegativo identificado como *K. aerogenes* por espectrometría de masas VITEK®MS (BioMérieux).

Se realizó el estudio de susceptibilidad mediante VITEK®2 (BioMérieux) para: ampicilina (CMI≥32 mg/L); amoxicilina/ácido clavulánico (CMI≥64 mg/L); piperacilina/tazobactam (CMI≥128 mg/L); ceftazidima (CMI≥64 mg/L); ceftriaxona (CMI≥64 mg/L); cefepima (CMI≤0,12 mg/L); ertapenem (CMI=0,25 mg/L); meropenem (CMI≤0,25 mg/L), amikacina (CMI≤1 mg/L); gentamicina (CMI≤1 mg/L); ciprofloxacino (CMI≤0,06 mg/L); trimetoprim/sulfametoxazol (CMI≤20 mg/L).

Tras 6 días de tratamiento con meropenem y mejoría clí-

Correspondencia:
Belén Cuadrado García
Servicio de Microbiología y Control de la Infección. Hospital Universitario de Canarias.
Ctra. Ofra S/N La Cuesta 38320, San Cristóbal de La Laguna. España
Tfno: 922679066.
E-mail: cuadradogarciabelen@gmail.com

nica, se desescaló a cefepime 2g/8h hasta completar 14 días. El decimoquinto día tras el ingreso se solicitó un TAC craneal tras la observación de movimientos anómalos, pico de presión arterial sistólica de 220 mmHg y hemiparesia izquierda.

El paciente sufrió deterioro de nivel de conciencia, se iniciaron medidas de confort, certificando su posterior fallecimiento.

Las meningitis postquirúrgicas conllevan alta morbilidad y mortalidad viéndose una mayor gravedad clínica en casos asociados a bacterias gramnegativas [4,5]. En un estudio de meningitis postquirúrgica por enterobacterias, la mortalidad fue del 23,2% siendo el ingreso en la UCI, la ventilación mecánica, la producción de β-lactamasas, la sepsis, un Glasgow≤8 y las comorbilidades factores de riesgo significativos para la mortalidad [6]. Los microorganismos más frecuentemente implicados son las enterobacterias, *Staphylococcus aureus,* estafilococos coagulasa negativos, *Pseudomonas aeruginosa* y *Acinetobacter baumannii* [4,7]. En este contexto, el uso de sistemas de PCR múltiplex permite adelantar el diagnóstico microbiológico respecto al cultivo. Aunque el BJIP está diseñado para infecciones articulares, gracias a la amplia variedad de microorganismos que incluye, supone una gran herramienta para el diagnóstico de meningitis posquirúrgicas en muestras de LCR. Aun así, es necesario determinar el patrón de sensibilidad del microorganismo dado el limitado número de genes de resistencia que detecta el panel.

En conclusión, este caso muestra la posible nueva utilidad del panel aportando un resultado precoz y mejorando el manejo del paciente. Es por esto que en los laboratorios de microbiología los paneles sindrómicos de PCR están adquiriendo relevancia en el diagnóstico precoz de las infecciones graves.

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BIBLIOGRAFÍA

1. Benito N, Mur I, Ribera A, Soriano A, Rodríguez Pardo D, Sorlí L, et al. The Different Microbial Etiology of Prosthetic Joint Infections according to Route of Acquisition and Time after Prosthesis Implantation, Including the Role of Multidrug-Resistant Organisms. J Clin Med. 2019; 8(5):673. https://doi:10.3390/jcm8050673
2. Codina MG, De Cueto M, Echevarría JE, Vicente D. Diagnóstico microbiológico de las infecciones del sistema nervioso central. Prats G, coordinador. Procedimientos en Microbiología Clínica. Cercenado E, Cantón R, editores. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, 2010.
3. Van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek A.T, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clinical Microbiology and Infection. 2016; 22 Suppl 3: S37-S62. https://doi:10.1016/j.cmi.2016.01.007
4. Zeinalizadeh M, Yazdani R, Feizabadi MM, Shadkam M, Seifi A, Dehghan Manshadi SA, et al. Post-neurosurgical meningitis; gram negative bacilli vs. gram positive cocci. Caspian J Intern Med. 2022; 13(3):469-474. https://doi: 10.22088/cjim.13.3.469.
5. Adapa AR, Linzey JR, Moriguchi F, Daou BJ, Khalsa SSS, Ponnaluri-Wears S, et al. Risk factors and morbidity associated with surgical site infection subtypes following adult neurosurgical procedures. Br J Neurosurg. 2021; 29:1-7. https://doi: 10.1080/02688697.2021.1905773
6. Shi YJ, Zheng GH, Qian LY, Qsman RA, Li GG, Zhang GJ. Longitudinal Analysis of Risk Factors for Clinical Outcomes of Enterobacteriaceae Meningitis/Encephalitis in Post-Neurosurgical Patients: A Comparative Cohort Study During 2014-2019. Infect Drug Resist. 2020; 13:2161-2170. https://doi: 10.2147/IDR.S252331
7. Panic, H., Gjurasin, B., Santini, M., Kutlesa, M., & Papic, N. Etiology and Outcomes of Healthcare-Associated Meningitis and Ventriculitis—A Single Center Cohort Study. Infectious Disease Reports. 2022;14(3): 420-427. https://doi.org/10.3390/idr14030045

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Artritis séptica por *Pasteurella multocida*

Carmen Piña Delgado[1]
María Nieves Carmona Tello[1]
Margarita Bolaños Rivero[1]
María del Carmen Lavilla Salgado[2]
Isabel de Miguel Martínez[1]

[1]Servicio de Microbiología, Hospital Universitario Insular-Materno Infantil de Gran Canaria, España
[2]Unidad de Enfermedades Infecciosas y Medicina Tropical, Hospital Universitario Insular-Materno Infantil de Gran Canaria, España

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Pasteurella multocida es un cocobacilo gramnegativo anaerobio facultativo y exigente, que forma parte de la microbiota orofaríngea de muchos animales y con frecuencia, produce infecciones de piel y tejidos blandos en humanos por inoculación mediante mordeduras o arañazos, especialmente de gatos y perros [1]. El género está formado por 20 especies, destacando *P. multocida*, aunque con menor frecuencia interviene *Pasteurella canis, Pasteurella stomatis y Pasteurella dagmatis* [2]. Causan un amplio espectro de enfermedades, desde infecciones locales hasta shock séptico. Infecciones graves, como osteomielitis, infecciones articulares e intraabdominales, bacteriemia, endocarditis y meningitis, pueden observarse en personas inmunocomprometidas [3].

Presentamos el caso clínico de un varón de 48 años que manifiesta infección osteoarticular complicada con shock séptico y necrosis de partes acras que conllevaron diversas amputaciones.

Como antecedentes personales destacan obesidad, asma, dislipemia y no presenta diabetes. Es trabajador de la construcción, convive con su esposa, un hijo de 23 años, tres gatos y un perro.

Acude al centro de salud con una úlcera cutánea de tobillo tras sufrir un accidente de moto donde se establece una pauta de curas sin la realización de prueba de imagen. Tras 9 días, sin ningún tipo de control de curas, acude al Servicio de Urgencias por dolor e inflamación del miembro inferior derecho y mala evolución de la úlcera, observándose fractura del maleolo posterior con artritis séptica del tobillo y celulitis perilesional con salida de abundante material purulento.

A las 20 horas de su llegada, presenta un deterioro clínico con fiebre, taquicardia e hipotensión que no mejora a pesar de fluidoterapia y requiere oxígeno que no necesitaba a su ingreso en Urgencias.

Ante la disfunción orgánica que los resultados analíticos corroboran: procalcitonina (19.15 ng/ml), proteína C reactiva (43.07 mg/dl), 144.000 plaquetas /µL, bilirrubina (1,99 mg/dl), creatinina (2,71 mg/dl), INR:1,95, IQ: 43%, LDH (5,46mmol/l), tensión arterial: 77/41mmHg y cumpliendo los criterios de sepsis con una puntuación en la escala de SOFA de 5, se extraen hemocultivos y se inicia antibioterapia empírica con piperacilina/tazobactam y daptomicina.

Ante los datos de shock séptico se consensúa con traumatología control urgente del foco infeccioso, realizándose artrotomía en tobillo derecho extrayendo muestras de líquido articular y absceso con abundante cantidad de contenido purulento denso, que son enviadas al laboratorio de Microbiología y procesadas según los criterios recomendados por la SEIMC.

Tras la intervención, presenta deterioro progresivo, ingresando en la Unidad de Medicina Intensiva por fallo múltiple orgánico precisando el uso de drogas vasoactivas a altas dosis.

Los 4 frascos de hemocultivos positivizan a las 8 horas de incubación. En la tinción de Gram de hemocultivos, líquido articular y absceso se observan cocobacilos gramnegativos. A las 24 horas de incubación se observa crecimiento de unas colonias grises brillantes y mucosas, catalasa y oxidasa positivas, en las placas de agar sangre y chocolate. Mediante espectrometría de masas (BD Bruker® MALDI Byotyper) se identificaron con alto valor de fiabilidad tanto a nivel de género como de especie [4] (score: 2.30) como *Pasteurella multocida*. El estudio de sensibilidad antibiótica se realizó mediante difusión en agar por E-test (Biomerieux®) en Mueller-Hinton sangre siendo susceptible a penicilina, cefotaxima, meropenem, linezolid, ciprofloxacino, levofloxacino, tetraciclina y trimetoprim/sulfametoxazol [EUCAST (European Comittee on Antimicrobial Susceptibility)] [5], con dichos resultados, se pauta antibioterapia

Correspondencia:
María Nieves Carmona Tello
Servicio de Microbiología, Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Avenida Marítima del Sur, s/n, 35016, Las Palmas de Gran Canaria. España
E-mail. mnievesct@gmail.com.

dirigida con meropenem y linezolid, desescalando a amoxicilina/clavulánico cuando los criterios infecciosos lo permitieron.

Al mes del ingreso, se realiza amputación de los dedos de la mano izquierda, parcial de los dedos del pie derecho e infracondílea del miembro inferior izquierdo por necrosis. Tras buena evolución y suspensión del tratamiento antimicrobiano es dado de alta a los dos meses y medio.

La bacteriemia por *P. multocida* se asocia a una alta tasa de mortalidad (14-31%) [6]. Escande y Lion [7] encontraron bacteriemia en el 11% de 958 casos de infecciones por *P. multocida*, otros estudios apuntan que el 50 % de rasguños, mordeduras y lamidas de perro y el 75 % de gato, presentan este microorganismo, por ello, debemos considerarlo ante personas con infecciones de tejidos blandos, expuestos a mascotas y comorbilidades subyacentes como diabetes, cirrosis, hipertensión, enfermedades malignas o estados de inmunosupresión [8].

En conclusión, es importante estar atentos ante la sospecha de una posible bacteriemia por *P. multocida* en personas con infección de tejidos blandos y contacto con animales de compañía durante las primeras etapas de su curso clínico, solicitando la extracción de hemocultivos, debido a la agresividad que el cuadro infeccioso puede producir [9].

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BIBLIOGRAFÍA

1. Bennett, John E., Raphael Dolin, and Martin J. Blaser, eds. Mandell, Douglas y Bennett. Enfermedades infecciosas. Principios y práctica. Elsevier Health Sciences, 2020.
2 de Cueto López M., Pascual Hernandez A. *Pasteurella multocida.* Control Calidad SEIMC.
3 Narsana N, Farhat F: Septic shock due to *Pasteurella multocida* bacteremia: a case report . J Med Case Rep. 2015, 9:159
4 Vega-Castaño S, Ferreira L, González-Ávila M, Sánchez-Juanes F, GarcíaGarcía MI, García-Sánchez JE, et al. Eficacia de la espectrometría de masas MALDI-TOF en la identificación de bacterias anaerobias. Enferm Infecc Microbiol Clin. 2012;30(10):597–601
5 The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022. http://www.eucast.org.
6 Chatelier E, Mahieu R, Hamel JF, Chenouard R et al. *Pasteurella bacteraemia*: Impact of comorbidities on outcome, based on a case series and literature review. Int J Infect Dis. 2020 Mar;92:89-96. doi: 10.1016/j.ijid.2020.01.003.
7 Escande F, Lion C. Epidemiology of human infections by *Pasteurella* and related groups in France. Zentralblatt Für Bakteriologie. 1993;279(1):131–39
8 Ranavaya J, Awadh H. A case of cat bite associated *Pasteurella multocida* prosthetic joint infection. IDCases. 2023 Mar 29;32:e01755. doi: 10.1016/j.idcr.2023.e01755.
9 Barsi ZE, Allen J, Meza A. More Than a Case of Cellulitis: *Pasteurella multocida* Bacteremia. Cureus. 2023 Mar 13;15(3):e36096. doi: 10.7759/cureus.36096.

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María del Mar Sánchez Suárez
Alicia Martín Roldán
María Rosa Cantudo Cuenca

Glecaprevir/pibrentasvir en combinación con ribavirina como terapia de rescate en hepatitis C crónica

Servicio de Farmacia, Hospital Universitario Virgen de las Nieves, Granada, Spain.

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En la era actual del tratamiento de la infección por el virus de la hepatitis C (VHC) con antivirales de acción directa (AAD), la terapia es segura, eficaz, de duración relativamente corta y curativa en la mayoría de los pacientes con tasas de éxito sobre el 95%. Pese a ello, una minoría de pacientes no responden a la triple terapia. La selección de virus multirresistentes asociada al fracaso terapéutico puede dificultar la eficacia de las terapias de rescate [1]. Por ello presentamos el caso de un paciente varón de 50 años derivado a nuestro centro para estudio pretrasplante hepático por hepatocarcinoma y cirrosis hepática por VHC genotipo 3a con estadio funcional de CHILD-PUGH A5 y MELD 7. Fue tratado con sofosbuvir/velpatasvir (SOF/VEL) 12 semanas en 2020 y con sofosbuvir/velpatavir/voxilaprevir (SOF/VEL/VOX) 12 semanas en febrero de 2021 en su centro de origen, sin respuesta a ambos tratamientos.

En la primera consulta se determina la carga viral en sangre (550.000 UI/mL log 5,74) y se lleva a cabo estudio de resistencias donde se detecta mutación M28V y L31M que confiere resistencia a todos los inhibidores de NS5A y Q80K en el estudio de NS3 por lo que es resistente a voxilaprevir (VOX). En cuanto al estudio de NS5B, no se detectaron variantes asociadas. Atendiendo al perfil de resistencias, las opciones posibles son un inhibidor de NS5B, sofosbuvir (SOF), un inhibidor de NS3/4A distinto a VOX, como grazoprevir (GZR) o glecaprevir (GLE), añadiendo o no ribavirina (RBV) a la terapia. Se descartó GZR por no estar indicado en genotipo 3. Se realizó una búsqueda bibliográfica donde se encontraron series de casos pacientes con fallo a SOF/VEL/VOX que precisaron tratamiento de rescate (Tabla 1). Los antivirales empleados fueron glecaprevir/pibrentasvir (GLE/PIB) junto con RBV, GLE/PIB + SOF + RBV, SOF/VEL/VOX + RBV y SOF/VEL + RBV [2-6]. Tras comprobar que no había interacciones significativas entre el tratamiento antiviral y su medicación habitual (omeprazol, risperidona, diazepam y desvenlafaxina), finalmente se prescribió GLE/PIB y RBV 600 mg cada 12 horas durante 16 semanas, duración recomendada en pacientes con genotipo 3 pretratados. El paciente obtuvo respuesta virológica sostenida (RVS) a las 12 semanas con resultado de ARN VHC en sangre indetectable.

En la actualidad no existen directrices clínicas que respalden la toma de decisiones a la hora de retratar a los pacientes en los que fracasa el tratamiento con SOF/VEL/VOX. El fallo a esta terapia antiviral se observa mayoritariamente en pacientes cirróticos infectados por genotipo 3 y 1a, no asociándose dicho fallo a ningún patrón específico de sustituciones asociadas a resistencia en NS3, NS5a y NS5b [5]. Con la evidencia disponible, aunque limitada, el retratamiento de estos pacientes, con esquemas basados en múltiples dianas como GLE/PIB + SOF + RBV o incluso el retratamiento con SOF/VEL/VOX + RBV durante 24 semanas, permite la RVS en un importante número de ellos. Además, también se ha demostrado una RVS del 100% en la estrategia de añadir RBV y/o SOF al tratamiento con GLE/PIB en pacientes que presentan un fallo terapéutico al mismo [3,7].

Actualmente no se puede demostrar que GLE/PIB + SOF + RBV sea superior a SOF/VEL/VOX + RBV para el tratamiento de rescate de múltiples fracasos de AAD [5]. Por lo tanto, se deben realizar más estudios sobre el tratamiento de los fracasos terapéuticos para aclarar esto. Por otro lado, aunque el estudio de resistencias antes de iniciar el rescate tras el fallo a SOF/VEL/VOX no se puede considerar obligatorio, conocer el genotipo de VHC y las resistencias, además de realizar una detallada evaluación del estadio clínico del paciente, contribuirán sin duda a conseguir curar a este subgrupo de pacientes con enfermedad avanzada.

Correspondencia:
Alicia Martín Roldán
Hospital Universitario Virgen de las Nieves.
Postal address: Avenida de las Fuerzas Armadas, 2, 18014, Granada
E-mail: aliciamartinroldan@gmail.com

Tabla 1 **Resultados búsqueda bibliográfica de pacientes con fallo a sofosbuvir/velpatavir/voxilaprevir**

Autor [Referencia]	Nº pacientes	Tratamiento rescate	RVS 12	N.º pacientes Genotipo 3	Tratamiento rescate	RVS 12
Bhattacharya *et al.* [2]	1	GLE/PIB + SOF + RBV	100%	1	GLE/PIB + SOF + RBV	100%
Wyles *et al.* [3]	23	GLE/PIB + SOF + RBV	96%	14	GLE/PIB + SOF + RBV	100%
Dietz *et al.* [4]	22	GLE/PIB (n=2) GLE/PIB + SOF+ RBV (n=15) VOX/VEL/SOF + RBV (n=4) VEL/SOF + RBV (n=1)	81%	12	VEL/SOF + RBV (n=1) VOX/VEL/SOF + RBV (n=2) GLE/PIB + SOF+ RBV (n=9)	88%
Martin *et al.* [5]	6	GLE/PIB + SOF + RBV	100%	2	GLE/PIB + SOF + RBV	100%
Meszaros *et al.* [6]	5	GLE/PIB + SOF + RBV	100%	3	GLE/PIB + SOF + RBV	100%

GLE: glecaprevir; PIB:pibrentasvir; RBV: ribavirina; RVS 12: respuesta viral sostenida a las 12 semanas; SOF: sofosbuvir; VEL: velpatavir; VOX: voxilaprevir

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BIBLIOGRAFÍA

1. Bhattacharya D, Aronsohn A, Price J, Lo Re V; AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023: ciad319. doi: 10.1093/cid/ciad319.
2. Bernhard B, Stickel F. Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: a case report. Z Gastroenterol. 2020;58(5):451-455. doi: 10.1055/a-1131-8058.
3. Wyles D, Weiland O, Yao B, Weilert F, Dufour JF, Gordon SC, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. J Hepatol. 2019; 70:1019–1023. doi: 10.1016/j.jhep.2019.01.031
4. Dietz J, Di Maio VC, de Salazar A, Merino D, Vermehren J, Paolucci S, et al. Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy. J Hepatol. 2021; 74:801–810. doi: 10.1016/j.jhep.2020.11.017
5. Martin MT, Patel S, Kulik L, Chan C. Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers high cure rate for hepatitis C virus retreatment in real-world settings. J Hepatol. 2021;75(1):251-254. doi: 10.1016/j.jhep.2021.02.024.
6. Meszaros M, Truchi R, Ouzan D, Tran A, Bourlière M, Pageaux G-P. Sofosbuvir, Glecaprevir, Pibrentasvir, and Ribavirin as a rescue therapy in difficult-to-treat HCV patients. Hepatology. 2021;74(4):2304-2306. doi: 10.1002/hep.31909
7. Aragri M, Milana M, Di Maio VC, Lenci I, Carioti L, Perno C, Fet al. Successful ongoing retreatment with glecaprevir/pibrentasvir + sofosbuvir + ribavirin in a patient with HCV genotype 3 who failed glecaprevir/pibrentasvir with both NS3 and NS5A resistance. Clin Microbiol Infect. 2020;26(9):1266-1268. doi: 10.1016/j.cmi.2020.03.022.