### CONSENSUS STATEMENT

### Antiviral treatment for SARS-CoV-2 infection in the current situation: a position paper of the Spanish Society of Emergency Medicine (SEMES)

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COVID-19 continues to pose a significant threat: mortality stands at nearly twice that of influenza, and the incidence rate is growing as the population's vaccination rate decreases, particularly in Spain and other areas of Europe. Given this situation, it is vitally important know whether medical protocols are consistent and appropriately implemented by health care staff in the interest of preventing possible inefficiency or inequity. Physicians from hospital emergency departments met to study their hospitals' usual clinical practices for managing SARS-CoV-2 infection and to determine their expert opinions on the use of antiviral agents. The participating physicians then reached consensus on evidence-based recommendations for strategies that would optimize emergency treatment.

Keywords: COVID-19. Antiviral agents. Nirmatrelvir-ritonavir. Remdesivir. Diagnosis. Therapeutics. Practice guidelines. Clinical protocols.

### Posicionamiento de la Sociedad Española de Medicina de Urgencias y Emergencias (SEMES) ante el tratamiento antiviral frente al SARS-CoV-2 en la situación epidemiológica actual

Actualmente, la COVID-19 sigue representando una amenaza significativa, con una mortalidad cercana al doble de la ocasionada por la gripe y con una incidencia variable debido a una disminución en la tasa de vacunación de la población, especialmente en el contexto europeo y español. Ante este panorama, es de vital importancia comprobar que los protocolos médicos están consolidados y son debidamente implementados por los profesionales sanitarios, con la finalidad de evitar posibles ineficiencias o inequidades. A través de reuniones con profesionales de urgencias se han observado las prácticas clínicas habituales en los servicios de urgencias hospitalarios para pacientes con infección por SARS-CoV-2, con la finalidad de comprender la perspectiva de estos profesionales acerca del uso de antivirales y, tras un consenso de expertos basados en la evidencia actual, se han generado estas de recomendaciones para poder enfocar estrategias que optimicen el tratamiento de los pacientes en estos servicios.

Palabras clave: COVID-19. Antivirales. Nirmatrelvir-ritonavir. Remdesivir. Diagnóstico. Tratamiento. Guías clínicas. Protocolos.

DOI: 10.55633/s3me/022.2024

### Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic, which is responsible for COVID-19 (coronavirus disease-2019),<sup>1</sup> has experienced an accelerated evolution since its first diagnosis in Wuhan on 31 December 2019.<sup>2</sup> After a health collapse in 2020 and numerous restrictions in the following months, we are now facing a new phase with measures adapted to the new situation.<sup>3</sup> There is greater knowledge of the disease which, together with the availability of vaccines and effective antiviral treatments, allows for

a drastic reduction in hospitalisation, severity and mortality, with a consequent decrease in public and medical concern.<sup>4-9</sup> Nevertheless, it is crucial to rigorously analyse current data and recognise that COVID-19 continues to represent a significant threat, with mortality close to double that caused by influenza<sup>10,11</sup> and with a possible increasing incidence due to a decrease in the vaccination rate of the population, especially in the European and Spanish context.<sup>12,13</sup>

In the Spanish case, the vaccination rates of the adapted booster doses in the population aged 60-69 years are 28%, in those aged 70-79 years 47% and in

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Información del artículo: Received: 10-11-2024 Accepted: 29-2-2024 *Online:* 1-4-2024

Editor in Charge: Agustín Julián-Jiménez those aged 80-89 years 60%.<sup>14</sup> In the case of hospitalisation, it can be observed that of the total number of confirmed cases in those over 60 years of age, 15-26% required hospitalisation.<sup>15</sup>

Against this background, it is of vital importance to check that medical protocols are consolidated and properly implemented by healthcare professionals to avoid possible inefficiencies or inequities.

It is well known that clinical practices can differ markedly between hospitals due to the uniqueness of each health institution and the diversity in the training and experience of its professionals.<sup>16</sup> This variation is accentuated when changes in diagnostic or therapeutic methods emerge,<sup>17</sup> a situation that has been constant since the beginning of the COVID-19 pandemic.<sup>17</sup> Perhaps the latest milestone in this regard is the introduction of antiviral treatments to the therapeutic regimen of patients. These treatments allow, in many cases, to treat patients on an outpatient basis, thus avoiding unnecessary hospitalisations.<sup>18</sup> Early treatment of patients with mild-moderate to severe COVID-19 with antivirals is considered a strategy that helps to change the course of the disease by reducing severity, mortality and the number of hospitalised patients.<sup>19</sup> Hospital emergency departments (EDs), which frequently see patients with COVID-19 who are candidates for antiviral treatment, are also particularly sensitive to changes in diagnostic and treatment protocols.

In Spain, the fragmentation of the health system into autonomous communities (ACs.) introduces another factor of variability.<sup>20</sup> Autonomous governments may establish their own clinical guidelines and recommendations, which could result in disparities in protocols.<sup>20</sup> In this sense, it is essential to ensure that all residents in Spain receive care of equal quality.

All this evidence suggests that clinical management in the ED may be heterogeneous. The aim of the present study was to analyse routine clinical practice in the ED to establish recommendations by expert consensus based on current scientific evidence.

### Methodology

### Scientific committee

The project was led by a scientific committee composed of 12 expert EPs with knowledge and experience in the clinical care of patients with COVID-19 from different hospitals in Spain.

### Experts

A group of 72 medical experts from different EDs was convened, representing a total of 70 hospitals from 4 autonomous communities (Andalusia, Catalonia, Community of Madrid, and Community of Valencia) representing 60% of the Spanish population. The participating centres were selected to be representative of the different levels of the Spanish healthcare system.



Figure 1. Project phases. SC: scientific committee.

### **Phases**

The project was carried out in a total of four phases (Figure 1). In the first phase, the scientific committee was formed, the overall project design was established, and a comprehensive literature review was conducted. This review gathered crucial information on the scientific evidence on the clinical management of COVID-19, especially focused on EDs. This period culminated in the creation of a 10-question questionnaire assessing current treatment and areas for improvement in EDs.

The second phase focused on establishing contact with leaders of the EDs located in the participating ACs. After presenting the project to them and obtaining their agreement to participate, they were provided with the online questionnaire, offering them the necessary time to provide detailed information.

The third phase was marked by a series of regional meetings where the experiences of the different centres were presented and subsequently a debate was opened in which those points where differences in the management of the COVID-19 patient were observed were discussed. The answers to the questionnaire were discussed and debated under the guidance of a member of the scientific committee.

Finally, in the fourth phase, the scientific committee met to pool and analyse the responses and findings from all regions. As a result, the manuscript was written, reviewed, and approved by all participants, which encompasses and presents the findings and results of the project.

### **Recommendations**

## 1. How to address barriers to antiviral administration in patients with mild disease?

### Recommendation

Training strategies should be established for emergency medical staff to clearly point out the eligible patients for antiviral treatment and the expected benefits in terms of mortality and reduced need for admission. This implies stratifying the risk of poor outcome in patients to detect those who are suitable for microbiological diagnosis and therapeutic decision making, as well as establishing appropriate treatment circuits for outpatients.

### Rationale

Several barriers to the prescription of antiviral treatment have been identified: 1) both in the medical field and among patients, there is a lack of awareness about the true severity of COVID-19, which leads to the fact that not enough diagnostic tests are currently being performed in at-risk populations; 2) the constant evolution of protocols and guidelines has generated confusion, increased by the lack of training of healthcare professionals; 3) this adds to the misperception of the futility of antivirals, the lack of knowledge about nirmatrelvir/ritonavir drug interactions and their management, the absence of a specific circuit for outpatient administration of remdesivir, and the absence of a robust system to monitor and evaluate the efficacy of treatment after administration.

### Lack of awareness

In the meetings held, a lack of awareness was detected among physicians, who underestimate the severity of COVID-19 due to the normalisation of the disease.<sup>21,22</sup> First of all, it should be recalled that, although mortality rates have decreased significantly, COVID-19 is still significant in a group of patients who remain at risk for a poor outcome of the infection.<sup>23</sup> A recent study in Switzerland showed a 7% mortality rate among patients hospitalised with COVID-19, twice that of influenza, despite the fact that COVID-19 patients were significantly younger.<sup>11</sup>

Secondly, infection can lead to the need for hospital admission. In older people, hospital admission carries several risks and adverse consequences. During even a brief hospitalisation, older patients may face complications such as delirium or functional impairment, which can significantly impact their subsequent quality of life<sup>24,25</sup> and the need to establish new social resources,<sup>26</sup> the risk of acquiring malnutrition and the development of sarcopenia.<sup>27,28</sup>

Currently, diagnostic testing for COVID-19 has been considerably reduced (Figure 2). There is a concern that patients with mild symptoms, but who are candidates for therapy, may not be being adequately diagnosed. The goal should be to reach diagnosis in at-risk populations to provide patients with rapid access to antiviral treatment, due to their limited therapeutic window.

### **Evolution of protocols**

Another of the barriers encountered is related to the changing and variable information on current protocols and guidelines. This is due to the constant evolution of these protocols without adequate accompaniment in the training of healthcare professionals, which makes it difficult for professionals to define the group of patients who could benefit from antiviral treatment.

### Utility of antivirals

There is a widespread perception that antiviral treatment is unnecessary because of the good outcome of patients with COVID-19, irrespective of host conditions. This assertion would presuppose active monitoring of the patient's progress by the ED, which is not carried out in routine clinical practice. However, such perceptions, far removed from the scientific evidence, have proved to be common among the participants in this study. To change this perception, it is necessary to train these professionals and disseminate the numerous studies that support the efficacy of antivirals against COVID-19 in the current context of the circulation of the omicron variant and high rates of immunisation in the population.<sup>4,6,29-31</sup>

In this regard, remdesivir has shown in mild patients (not requiring oxygen) a decrease in the relative risk (RR) of death and 30-day admission for any cause compared to placebo of 0.13 (95% CI: 0.03-0.59; P = .008). 30 Nirmatrelvir/ritonavir has shown lower hospitalization rates in patients aged 18-49 years, with a Hazard Ratio (HR) of 0.59 (95% CI: 0.48-0, 71), 50-64 years, with an HR of 0.40 (95% CI: 0.34-0.48); and in patients aged 65 or older, with an HR of 0.53 (95% CI: 0.48-0.58).<sup>8</sup>

A key component in the safe administration of nirmatrelvir/ritonavir is the management of drug-drug interactions.<sup>32</sup> In this regard, simplification of the process should also be sought, either by involving professionals from the hospital pharmacy service (HPS) or by using tools to help collate potential interactions (https://www. covid19-druginteractions.org).<sup>33</sup> If drug-drug interactions are properly managed, treatment with nirmatrelvir/ritonavir is highly safe.

On the other hand, if it is not possible to prescribe nirmatrelvir/ritonavir to a patient with mild disease, due to the presence of drug interactions, severe renal or hepatic insufficiency, or because the patient is in a therapeutic window between the 6th and 7th day, we must not forget that there is an alternative of administering remdesivir. This requires the existence of an adequate circuit for its ambulatory administration because it is an intravenous treatment.



Figure 2. Diagnostic tests for SARS-CoV-2 performed in Spain (data extracted from reference 64).

### 2. How to improve the degree of adherence in the emergency department to current clinical practice guidelines on the use of antivirals?

### Recommendation

It is essential to maintain stability in the clinical guidelines, without frequent changes, and for the physician to be familiar with both their content and their interpretation.

#### Rationale

The constant changes in the protocols for the management of patients with COVID-19 since the beginning of the pandemic have not been accompanied by adequate training programs. As a result, lack of adherence to these protocols can be a health problem. For example, regional meetings have revealed that not all healthcare professionals are fully aware of which profiles of patients with COVID-19 presenting to the ED should receive antiviral therapies. This situation could have been mitigated if clinical guidelines had maintained greater stability and if the necessary training programs had been implemented. The current scenario may represent a factor leading to inefficiencies in health management, potentially triggering unfavorable medical outcomes that could be avoided if the measures were adopted.

# 3. How to address heterogeneity or ensure therapeutic equity?

### Recommendation

It is essential to provide adequate training, combat COVID-19 fatigue among healthcare personnel and insist on the responsibility of these professionals to offer patients evidence-based medicine.

### Rationale

Among the participating hospitals, heterogeneity has been observed both in the administration of treatments and in the established circuits, resulting in inequity in the health services provided to patients. Heterogeneity in medical practices can arise due to a variety of reasons, such as variability in the interpretation of clinical guidelines, lack of updated training, and individual responses based more on experience than on current scientific evidence.<sup>34</sup> This heterogeneity can lead to inconsistencies in the medical care offered to patients in different institutions.<sup>35,36</sup> For example, the administration of treatments can vary according to the criteria of the treating physician, and the care circuits established in one hospital can differ considerably from those in another.<sup>35,36</sup>

These discrepancies in care, coupled with variations in available resources and staff training, can create inequities in medical care.<sup>37</sup> This inequity is not only counterproductive to the well-being of patients, but also runs counter to the fundamental principles of medicine and professional ethics.<sup>38</sup>

In addition, the fatigue factor that affects many healthcare professionals cannot be ignored.<sup>39</sup> This fatigue, resulting from months of dealing with the unprecedented pressure, stress, and demands of the pandemic, can impact their ability to make informed decisions and provide the best possible care.<sup>39</sup>

For all these reasons, the importance of providing adequate and continuous training for healthcare professionals and equipping them with the necessary tools and knowledge based on scientific evidence is emphasized. All these measures are essential to ensure that all patients receive a consistent and high-quality standard of care, regardless of the hospital where they are treated.

# 4. How can patients who are candidates for antiviral treatment be identified in the emergency department?

### Recommendation

To detect patients who are candidates for treatment, it is necessary to implement automated alert systems. In addition, it is essential to strengthen the training of ED professionals and simplify decision-making protocols.

#### Rationale

In medical settings, especially those with high demand for care such as the ED, efficient management of time and resources is crucial to ensure patient safety and health. Alert systems play a transcendental role in this area, acting as gatekeepers that prevent patients in critical situations from getting lost in the system or not receiving immediate attention. At present, many EDs already have this technological aid in various serious diseases, such as sepsis, infarction, and stroke, so that healthcare professionals are already accustomed to their use. It should also be noted that these codes not only identify the patient, but also serve to trigger a series of present procedures that optimize their medical care.

However, it will not be possible to implement these systems in all hospitals. In the absence of such systems, it is advisable to use other strategies to prevent or mitigate possible delays in the identification and treatment of these patients, and their consequent worse prognosis. In these cases, continuous and specialized training of ED staff becomes essential to compensate for the lack of such systems, providing them with the tools and knowledge to recognize and act quickly in the presence of patients who require it. Similarly, simplifying decision-making protocols can minimize confusion, ensure consistent and systematic care, and thereby improve patient outcomes.

## 5. Which patients with mild disease should receive antiviral treatment?

### Recommendation

Those susceptible to disease progression should receive antiviral treatment. There are different profiles: immunocompromised patients, elderly patients, patients with comorbidities or with incomplete vaccination status (having received fewer doses than recommended).

### Rationale

The strategy for determining which patients should receive treatment is based on current scientific evidence showing that the patient's immunological status, vaccination status, age and the presence of comorbidities are key predictors of disease progression (Table 1 and Figure 3).<sup>4,40-42</sup> For that reason, it is paramount to treat patients with mild COVID-19 who present with these clinical and demographic features while they are still in good clinical condition. Of course, it is essential to consider the therapeutic window, which varies between 5 (for nirmatrelvir/ritonavir) and 7 (for remdesivir) days depending on the drug.<sup>43,44</sup>

It should also be noted that the Spanish Agency of Medicines and Health Products (Spanish acronym, AEMPS) has ceased to establish specific conditions for the indication of treatment, which marks a significant change in clinical decision-making.<sup>45</sup> This translates into a more autonomous medical practice, where the physician is primarily responsible for evaluating and deciding the best treatment for his or her patient, based on the drug's technical data sheet and the guidelines provided by the various regional or hospital health committees.

In relation to incomplete vaccination status, that is, when the patient has received fewer doses of SARS-CoV-2 vaccine than recommended, it is important to note that there is concern about declining adherence to vaccination recommendations among the susceptible population.<sup>13,46</sup> If this trend persists, we should consider that more and more individuals may be at risk of progressing to severe COVID-19. In addition, evidence in the literature suggests that vaccine efficacy may decline over time, which could lead to a reassessment of what is considered a complete vaccination regimen as new studies are published.<sup>47</sup> Finally, in relation to vaccination status, it has been observed that in immunosuppressed patients, such as those treated with anti-CD20 antibodies or on dialysis, the response to the vaccine may be poor.48 It is therefore essential to adopt a more proactive approach in these cases by considering antiviral treatment as a crucial measure.49

# 6. What are the antivirals for the treatment of patients with mild disease?

### Recommendation

It is suggested to use nirmatrelvir/ritonavir as the first treatment option, and to resort to remdesivir as an alternative when the former cannot be administered.

#### Rationale

Recent data obtained in routine clinical practice demonstrate the effectiveness of antiviral drugs in preventing hospitalization, even with variants such as omicron. Both remdesivir and nirmatrelvir/ritonavir have demonstrated in a real-life setting efficacy close to those found in pivotal trials in preventing hospitalization or death: 99.2% for nirmatrelvir/ritonavir43 and 99.3% for remdesivir.<sup>30</sup> Similar results in the prevention of hospitalization or death have been described in a study carried out in Italy where 781 patients were treated with sotrovimab, remdesivir, nirmatrelvir/ritonavir, or molnupiravir.<sup>50</sup> In the same direction point to the results of a study conducted in 107 patients who were seen in the ED and received remdesivir, where 3 patients (2.8%) were eventually hospitalized and no mortality was reported.<sup>51</sup> Regarding nirmatrelvir/ritonavir, a recent retrospective study conducted in 470 patients showed that, of the 261 patients treated with the drug, it significantly increased viral clearance compared to delayed administration or placebo (P < .001).52 In the same vein, a paper that analyzed a cohort of 177. 545 patients, in which 8876 were treated with nirmatrelvir/ritonavir, showed a decrease in the rate of hospitalization and mortality in that group compared to the group that had not received

Table 1. Risk factors for progression of COVID-19

Chronic kidney disease: patients with glomerular filtration rate below 60 ml/min.

Chronic liver disease: patients with a classification on the Child-Pugh scale for severity of liver disease class B or C (decompensated liver disease).

**Chronic neurological disease:** multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, Huntington's disease.

Cardiovascular disease, defined as a history of any of the following: myocardial infarction, heart failure, angina pectoris with prescribed nitroglycerin, coronary revascularization grafts, percutaneous coronary intervention, carotid endarterectomy, and aortic bypass.

Cerebrovascular diseases: stroke, transient ischemic attack.

**Chronic lung disease:** high-risk COPD (post-bronchodilation FEV1 < 50% or dyspnea (mMRC) of 2-4 or 2 or more exacerbations in the last year or 1 admission); asthma requiring daily treatment.

Other pulmonary diseases amenable to lung transplantation: pulmonary hypertension, fibrosing lung diseases, diffuse interstitial lung disease, bronchiectasis.

Diabetes with target organ involvement. Obesity (BMI  $\geq$  35).

### Underweight Bajo peso (BMI $\geq$ 18,5).

COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV1: forced expiratory volume in the first second; mMRC: modified Medical Research Council dyspnea scale.



Figura 3. Algorithm for use of antiviral treatment in SARS-CoV-2 infection. eGRF: estimated glomerular filtration rate; IR: renal failure.

the drug (2.1% vs. 3.7%), with an odds ratio (OR) of 0.56 (95% CI 0.47-0.67). $^{6}$ 

Nirmatrelvir/ritonavir stands out in the treatment of mild COVID-19 as the only antiviral treatment available in oral formulation for these patients.<sup>43,44</sup> Despite its advantages, nirmatrelvir/ritonavir is not suitable for all patients and situations. Its use is contraindicated in patients with severe renal and hepatic insufficiency, and it has drug interactions that, although they can be guided by various tools (https://www.covid19-druginteractions.org/checker),53 are not always adequately managed by all professionals. Studies are currently evaluating the safety of using nirmatrelvir/ritonavir in patients with severe renal insufficiency but have not yet led to a change in the drug's label.<sup>54</sup> Polypharmacy in patients with multiple comorbidities increases the risk of interactions with ritonavir.<sup>32</sup> In such cases, during treatment with nirmatrelvir/ritonavir, it is essential to adjust, suspend or temporarily substitute certain drugs.

Another barrier to the use of nirmatrelvir/ritonavir is that, as a rule at present, the prescription validation process must be carried out by HPS. This requirement, although it guarantees safety, can lead to delays if an HPS specialist is not continuously available, sometimes extending this period up to 3 days, when the process takes place over the weekend.

Another aspect to consider is the therapeutic window of nirmatrelvir/ritonavir, which is 5 days from the onset of symptoms.<sup>44</sup> If this period is exceeded, remdesivir, with a therapeutic window of up to 7 days,<sup>43</sup> becomes the preferred option. Thus, when the above circumstances preclude the use of nirmatrelvir/ritonavir, remdesivir is the treatment of choice.

Recently, scientific evidence has been published that supports the use of remdesivir in patients with COVID-19 who present severe renal insufficiency,<sup>55</sup> even in those undergoing dialysis treatment,<sup>56</sup> and in patients with mild, moderate, or severe hepatic insufficiency,<sup>57</sup> which has led to the modification of its technical data sheet to authorize its use in these circumstances. However, given that it is a drug administered intravenously, for its application to be effective in this profile of patients who do not require hospitalization, it is essential to establish a well-defined administration circuit, guaranteeing an effective transition between treatments according to the patient's circumstances.

# 7. Treatment Circuits for Patients with Mild Disease

### Recommendation

All hospital centers should have a circuit for the administration of remdesivir for 3 days without the need for admission, with the optimum being that they receive the first dose in the ED and the following 2 doses in a day hospital specifically for patients with COVID-19 or in home hospitalization, depending on the characteristics of the patient.

### Rationale

Regarding treatment with remdesivir, a notable disparity has been observed in its administration circuit in the different hospitals, based on the responses of the participants. However, there is a common objective, which allows both the rapid prescription of the treatment and the non-hospitalization of the patient. There are experiences detected in which repeated doses were also carried out in the ED itself. However, this implies having a protocol and isolation infrastructures that are not available in all hospitals, so it is not the most recommendable option. The recommended circuit is to initiate treatment with remdesivir in the ED, and subsequent doses should be administered in a setting other than the ED, either in the hospital (specific day hospital) or through hospitalization at home (HaH).

The movement of patients with COVID-19 between different services, hospitals or on public transport to attend a medical appointment presents an added risk of spreading the virus that should be minimized. In this context, HaH offers a clear advantage and could be proposed as a first option whenever available. In any case, it is imperative to have a well-defined and optimized circuit that allows for the effective administration of remodivir, without compromising the safety of the patient, healthcare personnel and other users of the healthcare center. In addition, this circuit should ideally be available for the referral of patients from primary care who are not candidates to receive nirmatrelvir/ ritonavir.

With respect to nirmatrelvir/ritonavir, given its oral administration, its treatment circuit is simpler. The necessary treatment should be provided in its entirety from the ED, with instructions for the patient and caregivers for compliance.

It is essential to emphasize that the best time to treat patients presenting in the ED with mild COVID-19 is as early as possible and preferably when they are in good health. This statement is supported by several studies performed with both nirmatrelvir/ritonavir<sup>52</sup> and remdesivir,58 which show a better prognosis associated with early treatment initiation.

# 8. In patients requiring hospitalization, where and when to start antiviral treatment?

### Recommendation

Antiviral treatment in severe patients requiring hospital admission should begin as soon as possible, as in any other disease, in the ED itself.

### Rationale

Timely treatment of infectious diseases, such as COVID-19, is essential to optimize prognosis and improve clinical outcomes in patients. There is ample evidence that early treatment in severe infectious diseases improves the patient's prognosis, so its initiation should not be delayed until the patient is hospitalized. This disease, in its most severe manifestation, can lead to complications and, in the worst cases, death. Recent data provided by the Ministry of Health,<sup>59</sup> together with international research,<sup>11</sup> indicate that mortality rates in patients admitted for COVID-19 remain significant.

Therefore, based on this evidence and with the intention of ensuring the best clinical outcomes, early treatment is highly recommended. Supporting this criterion is the fact that treatment of diseases diagnosed in the ED is routinely started in the same department, and there is no clinical justification for this to be different for COVID-19.

# 9. Which hospitalized patients with COVID-19 should be treated?

### Recommendation

Patients with stereotypic disease or in the presence of decompensation of chronic respiratory or cardiorespiratory disease triggered by SARS-CoV-2 infection should be treated. At-risk patients with mild, symptomatic disease who are admitted for reasons other than COVID-19 and who are at risk of progression to severe disease should also receive antiviral treatment.

### Rationale

This recommendation is based on the various studies conducted to date, which include one clinical trial,<sup>60</sup> and several studies that have presented data from routine clinical practice. In total, these studies involve data from 85 276 patients, of whom 52726 have been treated with remdesivir.<sup>7,61,62</sup> These studies have shown that remdesivir can shorten recovery time in hospitalized adults with COVID-1960, decrease progression to need for ventilation with a RR of 0.84 (95% CI: 0.75-0.93, P = .001)<sup>7</sup> and improve survival with a RR of 0.91 (95% CI: 0.82-1.02, P = .12)<sup>7,60</sup> such that at 14 days a HR of 0.70 (95% CI: 0.62-0.78) and at 28 days a HR of 0.75 (95% CI: 0.68-0.83) is obtained.<sup>62</sup>

# 10. What is the antiviral of choice for patients who are candidates for treatment and are admitted to the hospital?

### Recommendation

The recommended treatment in patients admitted to hospital is remdesivir.

### Rationale

In this scenario, patient with COVID-19 requiring hospitalization, remdesivir is the only drug that has solid and specific studies related to its application in hospitalized patients due to COVID-19, both in the context of clinical trials,<sup>60</sup> and in studies with real clinical practice data.<sup>7,61,62</sup> Future studies could serve to expand the therapeutic arsenal in these clinical situations, but at the time of submission of this document remdesivir is the recommended treatment for patients requiring hospital admission due to COVID-19.

### Conclusions

Treatment of COVID-19 has evolved progressively since the pandemic began but is now more standard-

#### Table 2. Final recommendations of the document

| 1. How to deal with barriers to the<br>administration of antiviral drugs in patients<br>with mild disease?                                    | It is necessary to establish training strategies for emergency medical staff to clearly explain who are the susceptible patients to receive antiviral treatment and the expected benefits in terms of mortality and reduction of the need for admission. This implies stratifying the risk of poor evolution in patients to detect those who are suitable for microbiological diagnosis and make the therapeutic decision, as well as establishing appropriate treatment circuits for outpatients. |
|---|--|
| 2. How to improve the degree of adherence in<br>the emergency department to current clinical<br>practice guidelines on the use of antivirals? | It is essential to maintain stability in the clinical guidelines, without frequent changes, and for the physician to be familiar with both their content and their interpretation.   |
| 3. How to deal with heterogeneity or ensure therapeutic equity?   | It is essential to provide adequate training, fight COVID-19 fatigue among healthcare personnel and insist on the responsibility of these professionals to offer patients evidence-based medicine.   |
| 4. How can patients who are candidates for antiviral treatment be identified in the ED?   | For the detection of patients who are candidates for treatment, it is necessary to implement<br>automated alert systems. In addition, it is essential to strengthen the training of ED<br>professionals and simplify decision-making protocols.  |
| 5. Which patients with mild disease should receive antiviral treatment?   | Those susceptible to disease progression, who have different profiles: immunocompromised patients, elderly, those with accumulated comorbidities or with incomplete vaccination status.  |
| 6. What are the antivirals for the treatment of patients with mild disease?   | Nirmatrelvir/ritonavir is suggested as the first treatment option, with remdesivir as an alternative when the former cannot be administered.   |
| 7. Treatment circuits for the patient with mild disease.  | All hospital centers should have a circuit for the administration of remdesivir for 3 days without the need for admission, and it is optimal that they receive the first dose in the ED and the following 2 doses in a day hospital specifically for patients with COVID-19 or in home hospitalization.  |
| 8. In patients requiring hospitalization, where and when to start antiviral treatment?  | Antiviral treatment for severe patients requiring hospital admission should begin as soon as possible, as in any other pathology, in the ED itself.  |
| 9. Which hospitalized patients with COVID-19 should be treated?   | Patients with stereotypic disease or in the presence of decompensation of chronic respiratory or cardiorespiratory disease triggered by SARS-CoV-2 infection should be treated. At-risk patients with mild, symptomatic disease who are admitted for reasons other than COVID-19 and who are at risk of progression to severe disease should also receive antiviral treatment.   |
| 10. What is the antiviral of choice for patients<br>who are candidates for treatment and are<br>admitted to the hospital?                     | The recommended treatment in patients admitted to hospital is remdesivir.  |
| ED: Emergency Department of the hospital.   |  |

ized. The disease generally shows a good clinical course. However, there are groups at risk of progression to death or hospitalization that should be identified during emergency care for the prescription of antiviral treatment.

For the patient with mild disease and high risk of progression, there are very effective antivirals used in routine clinical practice, nirmatrelvir/ritonavir and remdesivir. Both have demonstrated efficacy in reducing the risk of progression.<sup>6,8,29-31,50,51</sup> Selection of the candidate patient for treatment depends on vaccination status, age, immunosuppression status and accumulation of comorbidities.<sup>61,63</sup> In this scenario, because of its oral treatment status and safety, nirmatrelvir/ritonavir is the first choice. However, it may present drug-drug interactions with other drugs or be contraindicated because the patient has renal or hepatic insufficiency and has a narrower therapeutic window than remdesivir. In this case, the patient should be treated with remdesivir. The second scenario is the patient with severe COVID, defined as those with respiratory failure or requiring hospital admission. In this scenario, remdesivir is the only one with randomized clinical trials showing its efficacy in reducing mortality in this population, especially if administered early from the onset of symptoms.7,62

The final recommendations are summarized in Table 2. Although this work has been carried out by a large group of expert emergency physicians who carry out their professional activity in 4 Autonomous Communities with different models of care and in hospitals at different levels of care, it cannot avoid the fact

that, since it is an expert opinion, its selection may present a motivational bias to participate in the study.

**Conflict of Interests Disclosure:** JGC has received honoraria and funding for continuing education programs from Pfizer, Gilead, MSD, and GlaxoSmithKline. CRL has received honoraria for conferences from Pfizer and Gilead and funding for conference attendance from Gilead. The other authors declare that they have no conflicts of interest.

Funding/Support: This project was funded by Gilead. However, this was an unconditional collaboration, and therefore the authors were not involved in the design, data collection, data analysis, or in the drafting or revision of the manuscript.

Ethical responsibilities: All authors have confirmed the maintenance of confidentiality and respect for patient rights in the document of author responsibilities, publication agreement and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Committee and with external peer review.

Acknowledgments: The authors would like to thank Antonio Javier Torres, PhD of Medical Statistics Consulting (MSC, Valencia), for his collaboration in the collection of data from the meetings and in the drafting of the manuscript in accordance with the code of good practice in publications (CPP3).

### Addendum

Members of the study who have participated in the meetings. En Andalucía: Manuel Aguilera Peña, Hospital de Montilla; Natalia Alonso Ortega, Hospital Santa Ana; Rafael Calvo Rodríguez, Hospital Universitario Reina Sofia; Rafael Canto Neguillo, Hospital de Alta Resolución Sierra Norte; María Paz Carmona, Hospital Universitario Virgen de las Nieves; José Cobo, Hospital Universitario de Jaén; Fernando Cuenca, Hospital la Merced; Mónica Dormido, Hospital Universitario Torrecárdenas; José Julio Egido, Hospital Universitario Puerto Real; César Fernández, Hospital Universitario de Jaén; Eva Fragüero, Hospital Universitario Poniente; Rafael Gallardo, Hospital Universitario San Agustín; José Alberto García, Hospital

Alto Guadalquivir; José Luis García Garmendia, Hospital San Juan de Alto Guadalquivil, jose Euis Garcia Garrieriana, rospital dan Jean Jean Dios del Aljarafe; Rocío Gil Alcaraz, Hospital Punta de Europa; Manuel Girona, Hospital de Baza; Tamara Gómez, Hospital de la Línea de la Concepción; Eissa Jaloud Saavedra, Hospital Universitario Infanta Elena; Marta Jiménez Parra, Hospital Universitario Virgen de la Victoria; Juan José Julia, Hospital Universitario Puerta del Mar; Elisa Lopera, Hospital Valle de los Pedroches; Salvador Mangas, Hospital Santa Ana; María José Marchena González, Hospital Universitario Juan Ramón Jiménez; Salvador Maroto Marín, Hospital Universitario Poniente; Rogelio Molina Ruano, Hospital Universitario San Cecilio; Isabel Morales Barroso, Hospital Universitario Virgen Macarena; Carmen Navarro Bustos, Hospital Universitario Virgen Macarena; Edelia Parejo, Hospital San Juan de la Cruz; Joaquín Peláez Cherino, Hospital Costa del Sol; Sol Puertolas, Hospital Universitario Virgen de Valme; Amelia Rio Ramos, Hospital de Huercal Overa de Almería; María Jesús Salas, Hospital San Juan de la Cruz; María Teresa Serrato, Hospital la Serranía; Alfredo Simón, Hospital de Antequera; Coral Suero Méndez, Hospital de la Axarquía; En Cataluña: Anna Coll, Hospital d'Olot i Comarcal de la Garrotxa; Jordi Company, Pius Hospital De Valls; Clara Gris, Hospital Residencia Sant Camil; Alexis Guzmán, Hospital Universitari Joan XXIII; Cristina Herranz, Hospital de Viladecans; Ferran Llopis, Hospital Universitari de Bellvitge; Andrés Martínez, Hospital Parc Taulí; Nuria Pomares, Hospital Universitari Mollet; Domingo Sanfiel, Hospital Santa Caterina; Anna Serrabou, Hospital de Sant Joan Despí; Juliana Villa, Hospital Universitari Sagrat Cor; En la Comunidad de Madrid: Virginia Álvarez, Hospital Universitario de Getafe; Esther Álvarez Rodríguez, Hospital Universitario Severo Ochoa; Sixto Aranda Sánchez, Hospital del Sureste; Carlos Bibiano, Hospital Universitario Infanta Leonor; Rosa Capilla, Hospital Universitario Puerta de Hierro; Helena de la Torre Marti, Hospital Universitario Puerta de Hierro; Carmen del Arco, Hospital Universitario La Princesa; Gema Delgado Cárdenas, Hospital Universitario de Fuenlabrada; Fátima Fernández Salgado, Hospital Universitario de Móstoles; Sara Gayoso, Hospital Comarcal del Escorial; Alejandro Martín Quirós, Hospital Universitario de la Paz; Roberto Penedo Alonso, Hospital Universitario Ramón y Cajal; Luis Pérez Ordoño, Hospital Universitario 12 de Octubre; Martín Ruiz Grinspan, Hospital Universitario del Henares; Octavio José Salmerón tal Universitario Gregorio Marañón; En la Comunidad Valenciana: Antonio Barceló, Hospital de Denia Marina Salud; María José Cantó, Hospital Universitari Arnau de Vilanova; María Ángeles Carbonell, Hospital General Universitari de Elda; Elena Díaz, Hospital Universitari Sant Joan d'Alacant; Antonio García Buigues, Hospital Marina Baixa; Federico Guerrero, Hospital General Duigues, Hospital Marina Balka, Federico Guerrero, Hospital General Universitari de Castelló; María Luisa López, Hospital Universitari Doctor Peset; Javier Millán, Hospital Universitari i Politècnic La Fe; José Noceda, Hospital Clínico Universitari de Valencia; Francisco Pérez, Hospital de Sagunto; Carles Pérez, Hospital Lluis Al-camirá de Vètirus Misici Alexiela Carvina de Valencia; canyís de Xàtiva; Ricardo Rubini, Hospital General de Valencia; Francisco Salvador, Hospital Francesc de Borja; Daniel Sánchez, Hospital Universitari de la Ribera.

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