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Third Pneumonia National Meeting

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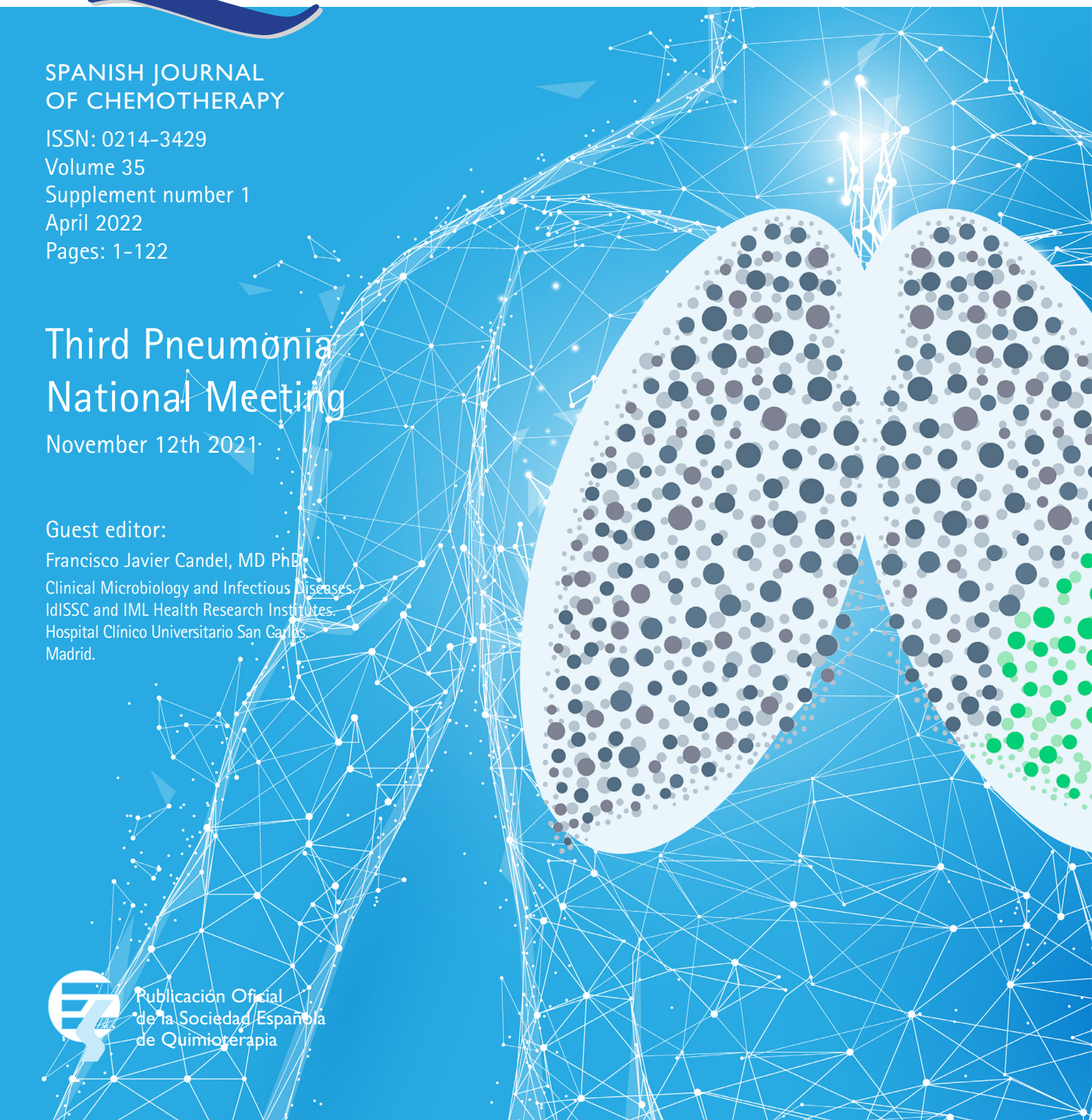

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Introduction

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Introduction to Third Pneumonia National Meeting (November 12th, 2021)

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Last November, for the World Pneumonia Day (November 12th), the Third Pneumonia National Meeting was held in the Marina of Valencia. This activity was developed by the Study Group of Infections in critical patients of the Spanish Society of Clinical Microbiology and infectious Diseases in conjunction with the Spanish Society of Pneumology and Thoracic Surgery. This is a scientific activity accredited and endorsed by the Spanish Society of Clinical Microbiology and infectious Diseases, the Spanish Society of Chemotherapy, the Madrid Society of Clinical Microbiology and the Spanish Society of Pneumology and Thoracic Surgery itself. This year the meeting, in virtual format, attracted more than 1,000 professionals from all the medical specialties related to this process.

The current supplement of the journal includes the abstracts in the form of mini-reviews with the contents of lectures given in the meeting. The reviews have been grouped into 5 topics to ensure a more didactic character. The first, *entitled current concepts in the diagnosis of pneumonia*, included topics such as the cytometric profile as a biomarker in the management of pneumonia, the need for rapid microbiological diagnosis of pneumonia in the critically ill patient, the value of syndromic platforms in the management of severe community-acquired pneumonia and the usefulness of chest ultrasound in the diagnosis and follow-up of pneumonia. The second covered *new antimicrobial alternatives in the treatment of pneumonia*, such as ceftobiprole, ceftaroline, cefiderocol, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam or imipenem-relebactam. The third section was dedicated to *pneumonia in patients with SARS-CoV-2 infection*. The topics developed in this section were ventilatory support in pneumonia, steroid therapy and antiviral treatment, immunotherapy, bacterial superinfection or respiratory functional sequelae after infection. The fourth section aims to *update special issues in pneumonia*. It reviews aspiration pneumonia, the top ten articles in pneumonia 2020-2021, the diagnostic and therapeutic approach to occupational pneumonias, the aetiology, diagnosis and treatment of pneumonia in immunocompromised hosts, the diagnostic and therapeutic approach to fungal pneumonia in the critically ill patient and the impact of vaccination on the epidemiology and prognosis of pneumonia. The last section included *some clinical cases of pneumonia* which, due to their aetiology or clinical profile, required a multidisciplinary approach. We hope you find it attractive and didactic.

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Current concepts in diagnosis of pneumonia

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Usefulness of monocyte distribution width (MDW) as a sepsis biomarker

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ABSTRACT

Sepsis is one of the main causes of mortality in the emergency department (ED), due to the fact that signs and symptoms are common to other acute diseases, and this can result in delayed detection. This diagnostic complexity has a huge impact on an entity in which early recognition determined treatment, as wells as enhance the patient's prognosis. Therefore, it is crucial to improve early identification. Different analytical tools arise from this approach, such as biomarkers: procalcitonin, C-reactive protein or MR-proadrenomedullin. In this review we will focus on a newer biomarker, the monocyte distribution width. The main objectives are to evaluate the usefulness of monocyte distribution width (MDW) in sepsis identification in ED, its limitations, and to compare it with other biomarkers.

Keywords: Biomarkers, Emergency department, Sepsis, Monocyte distribution width

INFECTIOUS DISEASES IN THE EMERGENCY DEPARTMENTS

Infectious disease is one of the most frequent reasons for consultation in the Emergency Department (ED), reaching around 15% of the patients assessed [1]. The profile of the patients attended are increasingly older with accumulative comorbidity, who are more frequently under immunosuppressive treatments, and have a higher prevalence of risk factors for infections by multidrug resistance microorganisms [1].

Lower respiratory tract infections are the main infection diagnosed and treated in ED. The incidence of community-acquired pneumonia (CAP) ranges between 2-15 cases/1,000 inhabitants/year, being higher in male patients, smokers, ≥75 years, with comorbidities or immunocompromised. Noteworthy that it represents the leading cause of death due to infectious disease in Western countries (10-14%) [2]. In EDs, 51% of CAPs correspond to patients aged ≥70 years, a subgroup with an increased diagnosis difficulty, greater clinical severity and short- and long-term mortality [3]. That is one of the reasons why it is the cause of most sepsis and septic shock treated [4], as well as the first cause of admission to intensive care unit [5]. There are great differences in diagnostic-therapeutic assessment in CAP, which is one of the reasons that explains the differences in admission rates (22-61%), the achievement of microbiological diagnosis, the request for complementary studies, and the choice of the antimicrobial regimen or the intensity of care offered [6]. Risk stratification is crucial to CAP patient management in ED in order to select the most appropriate care setting, including outpatient treatment, admission to a hospital ward or admission to an intensive care unit. Thus, clinical studies are currently focusing on searching for the most appropriate prognostic factors and risk stratification tools in respiratory medicine.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [7]. Patients with suspected infections presenting to the ED can potentially develop life-threatening conditions, so early detection of sepsis is the key to starting specific treatment and improving outcome. Nevertheless, sepsis is a heterogeneous syndrome and the detection during the initial assessments not only depends on site of infection, etiology, onset time, but also on the patient's profile (age, comorbidity and previous treatments). Despite the attempt to standardize the diagnosis, many controversies still exist. For this reason, the increasing value of those tools that can help physician with an early diagnosis is very important. Multiple studies, reviews and meta-analyses demonstrate the usefulness of biomarkers in EDs, especially in CAP [8].

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Different biomarkers emerged as a useful instrument for the early identification of sepsis, like C-reactive protein (CRP), procalcitonin (PCT) or MR-proadrenomodullin. According to this research line, a possible new biomarker emerges: monocyte distribution width (MDW). The aims of this review are: evaluate the utility of MDW in sepsis identification in ED, its limitations, and compare it with other biomarkers.

WHAT MONOCYTE DISTRIBUTION WIDTH IS?

MDW is a measure of the dispersion around the population mean, of the volume of monocytes in whole blood, obtained through the VCS (Volume, Conductivity, and Dispersion) technology [9]. It is a parameter calculated using an automated hematology analyzer that has enhanced cell counting capabilities through VCS technology. This improvement allows detection of morphological changes in immature and reactive cells, just as a microscopic evaluation of a peripheral blood smear would [10].

Sepsis is related to the balance of the pro-inflammatory and anti-inflammatory mechanism. Based on this knowledge, recent evidence supports that the monocyte could reflect early alterations in this inflammatory stage, since it undergoes morphological changes in inflammatory condition. Under this line of research, it is suggested that if these changes can be identified through VCS technology, it could be used as an early sepsis identification [9].

MONOCYTE DISTRIBUTION WIDTH COMPARE WITH CLINICAL SCORES

The perfect biomarker would be the one available at the admission in the emergency department. Due to the lack of this type of implement, different scores are used in daily medical practice. As reported in the Third International Consensus Definition for Sepsis and Septic shock (Sepsis-3), the recommended score were SOFA (Sequential Organ Failure Assessment) and qSOFA (Quick Sequential Organ Failure Assessment) outside the intensive Care Units. Furthermore, qSOFA score is accessible at the initial ED encounter. It is based on three criteria: tachypnea, altered mental status, and hypotension [7]. Despite the fact that it is easy to assess the compounding parameters, it is also common to find them in others acute illnesses. That is the reason why and accurate and reliable biomarker is needed to enhance sepsis suspicion.

Crouser et al. [11] compared the contribution of qSOFA score, and also SIRS (Systemic Inflammatory Response Syndrome) criteria, by their own in the early diagnose of sepsis, and also in contrast with the contribution of MDW alone. They also checked the improvement in the prompt detection of this entity using these scores along with MDW. The study supports that MDW improves the early recognition of sepsis as well as it is a complementary implement of timely detection of sepsis besides qSOFA and SIRS.

MONOCYTE DISTRIBUTION WIDTH COMPARE WITH OTHER BIOMARKERS

As aforementioned, sepsis disease is often not suspected on initial encounter. Therefore, until the laboratory parameters are obtained this entity it is sometimes not considered, which delays the diagnosis. Overall, in order to settle this suspicion an ordinary complete blood count is not enough, since it is confirmed by increase in sepsis biomarkers like procalcitonin, lactate, CRP.

Considering that MDW is a parameter obtained through a routine blood draw, whose result is obtained faster than other biomarkers, different studies arise to compare the reliability of this parameter in sepsis identification, in contrast to the biomarkers already used.

Agnello et al. [9] investigated the role of MDW as indicator of sepsis in the ED. An observational study was conducted, including consecutive adult patients divided into 4 groups: controls, non-infection SIRS, non-sepsis infection, and sepsis. Through an analyzed blood sample, the following parameters were determined: white blood cells (WBC); levels of CRP, and MDW. Regarding the results, MDW levels were higher in septic patients than in the others groups. In addition, it also revealed that there was significant statistic correlation between MDW and CRP. This correlation was higher than the one between MDW and WBC, or CRP and WBC. Furthermore, it was observed through receiver operating characteristic (ROC) curve analyzing sepsis prediction, that the area under the curve (AUC) was significantly higher for MDW, than CRP, showing an optimal diagnose accuracy of MDW.

Crouser et al. [12] developed a blinded prospective cohort study with two different ED population categorized as sepsis and non-sepsis infected patients. From blood collection, different parameters were obtained: mean neutrophil volume (MNV), neutrophil distribution width (NDW), mean monocyte volume (MMV), and MDW, as well as routine complete blood count (CBC). After establishing cut-off values for each one, MDW was the best discriminator of sepsis, based on AUC (0.79; confidence interval 95% 0.73 to 0.84). Additionally, the results provided showed a statistically significant added value for the association of MDW and WBC count (AUC 0.89) versus WBC alone (AUC 0.81). These results support the hypothesis that MDW could be used as a tool to improve early detection of sepsis on its own, as well as in conjunction with WBC count.

Subsequently, Crouser et al. [13] carried out a widespread study with a population of three EDs. It was also a blinded, prospective, cohort study, enrolling 2,158 subjects who were classified according to the Sepsis-2 criteria (control, SIRS, infection, and sepsis) and the Sepsis-3 criteria (control, infection, and sepsis). Through the examination of blood sample, the CBC and MDW values were obtained, analyzing these values according to the categorization carried out (Sepsis 2 and Sepsis 3 conditions). As it turned out before, it also concluded that MDW alone was sufficiently effective for early sepsis recognition, regardless of the sepsis criteria used. Moreover, in tandem with WBC increases the early identification of sepsis.

Regarding procalcitonin (PCT), Piva et al. [10] conducted a prospective observational study of adult patients admitted to an intensive care unit who were divided into 3 groups: non-septic, sepsis, and septic shock. As part of the clinical examination, not only CBC was analyzed, but CRP and PCT were also determined. Diagnostic performance in predicting sepsis was compared between PCT, CRP, and MDW, concluding that MDW was comparable to PCT, while it was better against CRP.

MONOCYTE DISTRIBUTION WIDTH CUT-OFF POINT

The different studies carried out to date differ regarding the best cut-off point for MDW as a predictor of sepsis: Crouser et al. [13] established that the best threshold to discriminate sepsis was 20, while Polilli et al. [14] determined that their best cut-off point was 21.9, and for Agnelle et al. [9] it was 23.5. Some of the reasons that could justify these variations would be the difference profile of the patients included in the studies developed in different setting as ED, infectious disease unit or in the intensive care unit are. On the other hand, it could also be related to the anticoagulant used in the sample (k3-EDTA; K2-EDTA). The discrepancy among different studies underline that more studies should be carried out to unify a reliable cut-off point.

MONOCYTE DISTRIBUTION WIDTH: FUTURE OPPORTUNITIES

Sepsis is a heterogeneous syndrome and the performance of biomarkers may be different depending on the patient's profile. In the ED, the patients who presents the greatest difficulty in terms of risk stratification and, therefore, whose diagnosis of sepsis may remain unnoticed, are those who are elderly, immunosuppressed, or undergoing biological therapies [15,16]. This patient condition is poorly represented in the studies carried out to date, which opens up an important line of research to assess the usefulness of MDW in these circumstances. Nevertheless, Lee AJ et al. [17] studied the utility of MDW in elderly patients concluding that MDW may be a promising hematological parameter to distinguish sepsis in elderly and therefore it may help clinicians in the prompt identification.

In addition, we must know the usefulness of MDW for the different sites of infection, such as pneumonia. Evidence on infection patterns is usually not reported in published articles. Only the Polilli et al. study [14] showed information on the type of infection, being lower respiratory tract infection represented in around 1 out of 3 patients, both in septic and non-septic patients included.

Whereas others biomarkers, such as PCT, have been shown to be useful in differentiating bacterial from viral infections, and it can be used for making-decisions regarding the use of antibiotics. It would be interesting not only to know how the etiology of the infection could condition the results of MDW, but also if its usefulness is maintained regardless of whether the infection is caused by bacteria, viruses or fungi. The study published by Piva E et al. [10] showed information based on the etiology of the infection. In particular, it is very interesting to note that there are important differences in MDW values between non-septic and septic patients, regardless of the etiology of the infection: septic patients without definitive identification, Gram negatives, Gram positive, virus, SARS-CoV-2, and fungi. However, there were no differences between the levels of MDW for the different causes of infection, which can be interpreted negatively (it would not be useful for antibiotic stewardship) or positively (similar utility regardless of the etiology).

Finally, it is also important to point out that the prognostic information, bacteraemia prediction, and monitoring antibiotic treatment response offered by other biomarkers have not yet been studied with the MDW [18,19].

CONCLUSIONS

The data suggest that incorporating MDW within current routine WBC counts may be of remarkable use for detection of sepsis. Further research is needed, but all articles support the hypothesis that, along with other biomarkers and clinical scores, MDW improves early detection of sepsis. MDW has the potential to become a fast, low-cost and accessible tool with a simple blood draw at ED admission, which would have a huge impact on the prompt recognition of sepsis. Therefore, multicenter studies should be expanded, considering that the current results are encouraging, and clinical trials should be designed in order to evaluate the impact of MDW value in the making-decisions in EDs.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Current concepts in diagnosis of pneumonia

Urgent need for a rapid microbiological diagnosis in critically ill pneumonia

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ABSTRACT

Severe lower respiratory tract infection is a common issue in Intensive Care Units that causes significant morbidity and mortality. The traditional diagnostic-therapeutic approach has been grounded on taking respiratory samples and/or blood cultures as soon as possible and starting empirical antibiotic therapy addressed to cover most likely pathogens based on the presence of the patient's risk factors for certain microorganisms, while waiting for the culture results in the following 48-72 hours to adequate the antibiotic treatment to the sensitivity profile of the isolated pathogen. Unfortunately, this strategy leads to use broad-spectrum antibiotics more times than necessary and does not prevent possible therapeutic failures. The recent development of rapid molecular diagnostic techniques, based on real time polymerase chain reaction (RT-PCR), makes it possible to determine the causative agent and its main resistance pattern between 1 and 5 hours after sampling (depending on each technique), with high precision, some of them reaching a negative predictive value greater than 98%, facilitating the very early withdrawal of unnecessary broad-spectrum antibiotics. Its high sensitivity can also detect unsuspected pathogens based on risk factors, allowing adequate treatment in the first hours of stay. This short review discusses the potential usefulness of these techniques in critically ill patients with lower respiratory tract infection and advocates their immediate implementation in clinical practice.

Keywords: Rapid diagnostic tests, RT-PCR, Multiplex PCR, Xpert, critically ill, Lower respiratory tract infection, Community-acquired pneumonia, Hospital-acquired pneumonia, Ventilator-associated pneumonia, Antibiotic stewardship, Empirical treatment

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INTRODUCTION

Both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), remain one of the leading causes of intensive care admissions or prolonged hospital stay and are related with substantial mortality.

Classically, when CAP/HAP/VAP are suspected, particularly in severe cases, promptly initiation of empirical antibiotics (very often two or more), based on the most likely involved pathogens, is recommended followed by de-escalation to a narrower spectrum pathogen-directed antibiotic once the causative agent has been isolated in microbiological culture [1-3]. However, this classical approach does not guarantee giving each patient the best antibiotic from the start, while many patients result overtreated and very few times a real early de-escalating strategy is implemented because the standard cultures are very frequently negative [4]. Over the last few years different rapid diagnostic tests (RDT) based on real-time polymerase chain reaction (RT-PCR) have emerged allowing to identify, in around 60 minutes, the etiologic agent and/or its main mechanism of resistance in a respiratory sample [5-9].

SARS-CoV-2 pandemic has highlighted the importance of implementing RDT capable of detecting the virus in a nasal-pharyngeal or respiratory sample [10], avoiding unnecessary antibiotics in many cases and this will be even more important when the pandemic ends as sporadic cases will come up. In fact, the use of multiplex RDT in respiratory samples reveals a significant number of viruses as etiological agents in CAP and these RDT detect 23.6% more pathogens than traditional culture techniques [11].

The potential utility of this new technology is enormous, particularly in severe cases of HAP/VAP, where it could allow not only giving the most appropriate antibiotic from the beginning, but also withdraw unnecessary drugs, preventing late resistance and adverse events. Implementing a new strategy

of rapid testing would be the first step for a real antimicrobial stewardship program defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration".

It is worth noting the importance of knowing very well the limitations of the particular RDT that is being used because those microorganisms not included in the panel, obviously cannot be ruled out. From this perspective, RDT should be considered as a complementary tool in adjunction to standard culture and clinical judgment to allow for an earlier pathogen-directed therapy.

Because some of these RDT have been developed to identify the most frequent CAP pathogens (viruses and bacteria), while others have been designed to detect microorganisms and bacterial resistance genes more commonly involved in HAP/VAP, this brief review will discuss how the implementation of these RDT could improve the correct daily use of antibiotics, saving unnecessary drugs, and potentially the outcome of severe CAP and HAP/VAP separately.

COMMUNITY ACQUIRED PNEUMONIA

Among European adults, CAP has an annual incidence of 1.07–1.2 per 1000 person-years, rising to 14 per 1000 person-years in those older than 65 years [12]. In USA, CAP is estimated to cause ~1.5 million hospitalizations and ~100,000 deaths each year [13]. CAP-related mortality in those patients admitted to Intensive Care Units (ICU) was approximately 30% before the SARS-CoV-2 pandemic but it has gone up to 35–50% in COVID-19 patients who require invasive mechanical ventilation [3].

Although there is increased recognition of the role of viral pathogens in CAP, currently, the empiric antibiotic therapy for severe cases, is based on international guidelines [1] which recommend using a macrolide or a respiratory fluoroquinolone in combination with a β-lactam to cover the most frequent pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae, Mycoplasma pneumoniae*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Legionella* spp., *Chlamydophyla pneumoniae*, and *Moraxella catarrhalis*. The coverage for PES pathogens (*Pseudomonas aeruginosa*, *Enterobacteriaceae* with extended-spectrum β-lactamases -ESBL-, and methicillin-resistant *S. aureus* -MRSA-) should only be initiated if "risk factors" are present because of the low prevalence of these pathogens, but this decision is not always easy because failing with the initial empiric treatment has been associated to worst outcome [14]. A Spanish retrospective study [15] with 1.597 CAP patients reported a 6% incidence of PES pathogens. Other study found that enteric Gram-negatives, such as *P. aeruginosa*, can be isolated in up to 2% of identified CAP microorganisms and are usually present in patients with prior structural lung disease, those who are on corticosteroids, have recently received antibiotic therapy or are in septic shock at admission [16]. Regarding MRSA, a multicenter, prospective surveillance study of 2.259 adults hospitalized with CAP, identified 1% with MSSA and 0.7% with MRSA. Chronic hemodialysis was more common among patients with MRSA (20%) than pneumococcal (2.6%) CAP. Nevertheless, clinical features at admission were similar, including concurrent influenza infection, hemoptysis, multi-lobar infiltrates, and prehospital antibiotics. Patients with MRSA had higher mortality (13.3% vs 4.4%) [17]. The Global initiative for MRSA pneumonia (GLIMP) study found a prevalence of confirmed MRSA in CAP patients of up to 3%, and MRSA was isolated mainly from patients with a prior MRSA infection or colonization, recurrent skin infections, or those with severe pneumonia [18].

However, the prevalence and risk factors for CAP related to MRSA may vary widely among regions. A study performed in the Pays de la Loire region in France [19] to determine the demographic characteristics of MRSA carriers in the community and to assess their risks factors and possible past hospitalization history, found 15% incidence rate of MRSA carriers. The isolates were most frequently recovered from skin and soft tissue infections (41.2%), urine (38.3%), genital samples (8.3%) and sputum (1.9%). Other pathological samples represented 10.3%, mainly from the ear-nose-throat sphere. Among the 313 patients who answered a questionnaire, 36 (11.5%) had none of the risk factors included in the questionnaire, such as home care, hospitalization during the preceding 12 months, and the presence of chronic cutaneous lesions.

In a systematic review and meta-analysis of Asia-Pacific region [20] the ranges of prevalence and characteristics associated with CAP-MRSA carriage varied from India (16.5%-23.5%), followed by Vietnam (7.9%) and Taiwan (3.5%-3.8%).

Because of the difficulties to predict the etiologic agent in severe CAP, some scores have been proposed to guide the empiric treatment, such as the PES score [15] (Table 1).

The decision to empirically treat these pathogens should be reserved for patients at high risk (i.e., PES score ≥5 points).

Table 1 PES score

Variables	Points
Age > 65 years	1
Male	2
Previous antibiotic use	2
Chronic respiratory disorder	2
At Emergency	
Consciousness impairment or aspiration evidence	2
Fever or shivers	-1

Low risk Multi Drug Resistant (MDR) score: ≤1; Medium risk MDR score: 2-4; High risk MDR score: ≥5. PES (*Pseudomonas aeruginosa, Enterobacteriaceae* extended spectrum β-lactamase-positive, and methicillin-resistant *Staphylococcus aureus*).

However, the clinician's fear of failing in the initial treatment of severe CAP, particularly in those patients in shock, leads to overuse broad-spectrum antibiotics such as antipseudomonal ß-lactams, vancomycin or linezolid. In the aforementioned study of 2,259 hospitalized adults with CAP [17], besides the very low prevalence of MRSA (0.7%), almost a third of the patients received anti-MRSA antibiotics. Therefore, there is an urgent need to improve this strategy.

Implementing RDT in the initial approach of severe CAP could contribute to save broad spectrum antibiotics, ruling out MRSA even in those patients with high PES score where *S. pneumoniae* is a frequent causative microorganism. Conversely, a few patients in shock and multiorgan failure with low PES score might benefit from a RDT because, although very unlikely, the impact of not treating a potential MRSA within the first hours would be detrimental. This may be particularly useful in regions with high prevalence of community MRSA carriers.

Very interestingly, a study performed in 212 hospitalized adult patients with CAP in Taiwan, showed a greater number of etiological agents identified when RDT were used. Bacterial pathogens were detected in 106 (50%) patients, viruses in 77 (36.3%), and fungal pathogens in 1 patient (0.5%). The overall detection rate (culture and molecular testing method) was 70.7%. Traditional microbial culture yielded positive results only in 36.7% while molecular testing in 61.3%. The most common pathogens were influenza (16.1%), *Klebsiella pneumoniae* (14.1%), *P. aeruginosa* (13.6%), human rhinovirus (11.8%), and *S. pneumoniae* (9.9%). Multiple pathogen co-infections accounted for 28.7%, of which co-infection with *K. pneumoniae* and human rhinovirus comprised the largest proportion [11].

Several studies performed in patients with lower respiratory tract infections (LRTIs) consistently find that microbiological documentation is almost twice as high using RDT compared to the standard method due to the higher sensitivity of the RDT. This is an advantage for patients treated with antibiotics prior to sampling but it also needs a cautious interpretation because RDT might detect nucleic acids from dead pathogens not involved in the current pneumonia episode leading to an overtreatment of non-viable microorganisms. Bearing these limitations in mind, different studies, most of them observational/retrospective, show that empirical treatment when RDT are used in LRTIs might be modified more than 50% of the time, mainly to de-escalate, although there are too few studies in CAP, particularly in severe cases, to draw robust conclusions about the impact of routinely RDT use on outcome (Table 2).

Gadsby NJ et al [21] studied respiratory samples from 323 adults with radiologically confirmed CAP. Specimens were cultured as per routine practice and also tested with fast multiplex real-time PCR assays for 26 respiratory bacteria and viruses. *H. influenzae* and S. pneumoniae were the most frequently agents detected. Viruses were present in 30% of cases; 82% of these were codetections with bacteria. Most (85%) patients had received antimicrobials in the 72 hours before admission. Of these, 78% had a bacterial pathogen identified by PCR but only 32% were culture-positive (P <.0001). PCR detected significantly more *H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus, E. coli*, and *K. pneumoniae* than standard culture-based methods. Molecular testing results were not released to the attending physician, but they could have had the potential to lead to de-escalation in number and/or spectrum of initial empirical antibiotic agents in 247 (77.2%) patients and to escalate in number and/or spectrum of antibiotic in 19 (5.9%) patients. The majority of the potential de-escalation events were related to switching from amoxicillin-clavulanate to narrower-spectrum agents such as amoxicillin and doxycycline in cases where *S. pneumoniae* or *H. influenzae* were detected by PCR and to withdraw clarithromycin in cases where atypical bacteria were not identified by PCR.

Quite similar results were found by Monard C et al [22]. They retrospectively studied 150 pneumonia episodes (54 CAP, 68 HAP, 37 VAP). In 37 out of 54 (69%) CAP episodes an expert committee considered the empirical treatment could change, mainly to deescalate to a narrower spectrum drug or stopping a companion antibiotic (37%) but also to escalate in 15% of the time.

Clinical metagenomics uses next generation sequencing of total nucleic acid from clinical samples to detect all the microbes simultaneously. The routinely application of this technology is still being validated but nanopore sequencing platform (Nanopore, Oxford, UK) has proven its ability to rapid LRTI pathogen detection [23]. Mu S et al [24] evaluated the clinical performance of rapid nanopore-sequencing based metagenomics test for diagnosis of bacterial pathogens in LRTIs. Among six different presentations of LRTIs, 171 bronchoalveolar lavage fluid (BAL) and 121 sputum samples were collected from 292 hospitalized patients. The turnaround time (from sample registration to result) for the rapid metagenomics test was 6.4 $\pm$ 1.4 hours, compared to 94.8 $\pm$ 34.9 hours for routine culture. Compared with culture and real-time PCR validation tests, rapid metagenomics achieved 96.6% sensitivity and 88% specificity and identified pathogens in 63 out of 161 (39.1%) culture-negative samples. Among those most common pathogens (*S. pneumoniae, H. influenzae*, and *M. catarrhalis*), rapid metagenomics detected 37 cases while traditional methods identified only 13 cases. Interestingly, rapid metagenomics detected 38 anaerobic bacterial species in 49% samples while none of them were identified by culture techniques. Although these results must be cautiously interpreted because some of the anaerobic bacteria may be contaminants from the upper respiratory tract, correlation between enriched anaerobes and lung abscess was observed by Gene Set Enrichment Analysis. If the results of the metagenomics test had been used to guide therapy, 33 patients might have had their empiric therapy de-escalated compared to 1 using standard culture. This new technology can be very helpful in cases of aspiration pneumonia and lung abscesses, in addition to critical patients with unexplained respiratory failure or those immunocompromised patients who are infected by uncommon pathogens not covered by conventional methods.

The study published by Qian Y et al [25] tested, with the FilmArray Respiratory Panel, respiratory samples from 112 hos-

Table 2 Potential implications of rapid diagnostic tests on the CAP empirical treatment

Author	Study type	Aim	Population	Assay	Result
Monard C et al.[22]	Retrospective multicenter, in 4 French university hospitals	Relevance of rapid multiplex PCR test to guide antimicrobial therapy.	150 pneumonia episodes (CAP = 54, HAP = 68, VAP = 37)	Rapid multiplex PCR	Proportion of potential antibiotic modifications: in VAP (87%), in HAP (79%) and CAP (69%) Modification of the empirical treatment for CAP: de-escalation in 37%, escalation in 15%, no change in 32%, undetermined in 17%.
Shengchen D et al.[28]	Single center randomized controlled study in China	To evaluate duration of IV antibiotic, LOS, cost of hospitalization and de-escalation.	800 patients with LRTI 398 allocated to POCT and 402 to standard RT-PCR	FilmArray Respiratory Panel as POCT vs Routine RT-PCR	Reduce IV antibiotic use, LOS and costs in hospitalized patients. More patients in the intervention group achieve de-escalation.
Gadsby NJ et al.[21]	Retrospective, in two United Kingdom hospitals	Utility of comprehensive molecular diagnosis approach.	323 CAP patients	Fast multiplex PCR for 26 pathogens	De-escalation in number and/or spectrum in 77% of patients, escalation in 5.9% and no change in 16.9%.
Huang AM et al.[29]	Observational study in 8 United States hospitals	Potential impact on modifications to antimicrobial therapy.	LRTI Respiratory samples (57 BAL, 48 sputum) from unique patients	FIlmArray LTRI Panel compared to SOC methods including bacterial culture and PCR based on standard laboratory	The most common type of potential intervention was antimicrobial de-escalation in > 50% of patients, using FilmArray LRTI Panel
Qian Y et al.[25]	Single center, prospective cohort in China compared with a previously not tested cohort	Clinical impact of FilmArray on unexplained pneumonia compared with conventional methods.	Unexplained pneumonia (67.4%CAP, 32.6% HAP): 112 patients prospectively tested vs 70 as control group	FilmArray Respiratory Panel	Significantly lower antibiotic/antifungal use in the intervention group. Significant higher antiviral treatment in the interventional group.
Mu S et al[24]	Single center, prospective cohort in China	To evaluate the clinical performance of a commercial rapid metagenomics test.	292 LRTI (51% in ICU: CAP = 83 HAP = 66 Other = 143	Rapid nanopore-sequencing metagenomics test	Hipothetical impact of metagenomics test proposed antibiotic de-escalation
Maataoui N et al.[26]	Single center, observational and retrospective study in Paris (France)	To evaluate the performance and the impact of the BioFire FilmArray Pneumonia plus panel	112 respiratory samples from 67 COVID-19 ICU patients suspected of bacterial coinfections	BioFire FilmArray Pneumonia Panel Plus	Modification of treatment in 50%. Positive tests led to antibiotic initiation or adaptation in 15% of episodes and de-escalation in 4%. When negative, 28% of episodes remained antibiotic-free (14% no initiation, 14% withdrawal).
Verroken A et al.[27]	Single center, prospective cohort in Belgium	To investigate the respiratory co-infection rate in COVID-19 critically ill and its impact on antibiotic management.	32 ICU COVID-19 patients	FilmArray Pneumonia Panel Plus Test (FA-PNEU)	Speeded-up antibiotic modification in 46,9% of patients.

CAP: community acquired pneumonia, LRTI: lower respiratory tract infection. HAP: hospital acquired pneumonia. VAP: ventilator associated pneumonia. LOS: length of stay. IV: Intravenous. POCT: point-of-care test. RT-PCR: real-time polymerase chain reaction. ICU: Intensive Care Unit. SOC = Standard of care

pitalized patients with unexplained pneumonia (75 CAP and 37 HAP) between October 2016 and March 2018. The most frequently found pathogens were Influenza A/B (47.3%). They recorded the demographic characteristics of these patients and their clinical data and were compared with a historical control cohort of 70 patients, who were hospitalized between October 2014 and March 2016, using the same inclusion criteria. The interventional group received significantly more antiviral treatment (oseltamivir and acyclovir) and the adjustment of antibiotics was recorded more frequently (69.6% vs 5.1%) compared to control group. This study suggests again, although with important limitations as a result of its design, that the RDT may

assist in clinical decision making, reducing unnecessary antibiotic usage in the treatment of pneumonia and starting earlier specific treatment in some cases.

Finally, special mention deserves COVID-19 pandemic where an accurate use of the antibiotic treatment, particularly in critically ill patients, is challenging. In this clinical setting, RDT can help improve antibiotic stewardship programs.

A French study [26] tested 112 respiratory samples from 67 COVID-19 ICU patients suspected of having bacterial coinfections with the BioFire® FilmArray® Pneumonia plus Panel. Among the 8 suspicions of CAP, for which all patients were treated, the positive RDT result led to a de-escalation and the 7 negatives to 3 antibiotic withdrawals and 4 continuations. Regarding the 104 suspected episodes of HAP/VAP, 36 RDT results were positive and 68 were negative. Among positives, in 36% (13/36) antibiotic treatment was initiated, in 8% (3/36) antibiotic therapy was modified, and in 4 (11%) was de-escalated. In one episode, neither the pre nor the post RDT, antibiotic treatment was adequate because of the presence of an unexpected *Stenotrophomonas maltophilia* not identified by the panel. Among negatives, 24% (16/68) remained antibiotic-free and 13 (19%) led to antibiotic withdrawal. Although in 57% (39/68) episodes, antibiotics were maintained due to severe sepsis (n = 20), infection from another site (n = 9), continuation of previous treatment (n = 7), or severely immunocompromised patients (n = 3), RDT produced antibiotic changes in 38/112 (34%) episodes.

Other interesting study performed in 32 COVID-19 ICU patients identified 13 (40.6%) cases with a bacterial co-infection [27]. The most frequently identified bacteria with significant genome copies were S aureus (one of them MRSA), H. influenza, and M. catarrhalis. None of the 32 RDT identified atypical bacteria neither other respiratory viruses. Direct communication of RDT led to speeded-up antibiotic modifications in 15/32 (46.9%) patients. Once again, the use of RDT reveals to be a key element of the antimicrobial stewardship strategy in COVID-19 severe disease.

HOSPITAL ACQUIRED PNEUMONIA AND VENTILATOR ASSOCIATED PNEUMONIA

Lower respiratory tract infections (LRTIs) such as HAP/VAP are associated with a significant increase in morbidity and mortality, even higher when effective antibiotic treatment is delayed [30]. Choosing the adequate empiric antibiotic for HAP/VAP is more challenging than for CAP because of the increased number of MRSA and potential difficult to treat antibiotic-resistant Gram-negative pathogens.

International guidelines advocate the empirical use of broad-spectrum antibiotics including carbapenems, when the patient has risk factors for MDR pathogens, such as previous colonization by MDR pathogens, has previously received antibiotics, or VAP develops after 5 days on mechanical ventilation. Furthermore, in those patients in ICUs where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, patients in an ICU where local antimicrobial susceptibility rates are not available, patients who are in septic shock at time of VAP, suffered ARDS preceding VAP, or they were receiving acute renal replacement therapy prior to VAP onset, should be empirically receiving 2 antipseudomonal antibiotics from different classes and anti-MRSA coverage [2]. Unfortunately, these risk factors are very common among critically ill patients and this strategy leads to overtreatment without ensuring full adequacy due to the potential MDR carbapenemase-producing pathogens.

Implementing a new strategy based on RDT might reduce the uncertainty of the empirical treatment, optimizing the antimicrobials stewardship programs in this setting (Table 3).

Interestingly, based on the high negative predictive value (NPV) of MRSA nasal colonization for developing MRSA pneumonia, some hospitals have implemented a protocol, as part of the antimicrobial stewardship program, to inform the staff about the usefulness of testing some patients for nasal MRSA before prescribing anti-MRSA in cases of pneumonia and to consider withdrawal of MRSA coverage when the RDT result is negative. In a normal basis, the RDT result is displayed in the patient´s electronic medical record and then the attending physician can consider stopping anti-MRSA antimicrobials following the protocol, unless other indication to keep them exits. Furthermore, the clinical pharmacist can order MRSA nasal PCR testing without a direct physician order when a patient receives a prescription of vancomycin or linezolid for suspicion of pneumonia. Once this protocol was implemented, a retrospective study was designed to evaluate the impact of a pharmacist-initiated MRSA nasal PCR protocol (PCR group) on pneumonia therapy compared with a routine schedule (Pre-PCR group). In the Pre-PCR group, 138 patients met the inclusion criteria, while 72 patients were included in the PCR group. There were no significant differences between the 2 groups except for higher ICU admission in the Pre-PCR group and more cases of HAP in the PCR group. There were no VAP cases in either study group. All patients eligible for study received vancomycin. Compared with the Pre-PCR group, the mean duration of IV vancomycin in the PCR group was 1.1 days shorter (2.5 ± 1.3 days vs 1.4 ± 1.2 days, $P < .001$). Among the 72 patients in the PCR group, 45 (62.5%) MRSA nasal PCR orders were placed by a clinical pharmacist while the remainder were ordered by an attending physician. There were 63 (87.5%) patients with a negative MRSA nasal PCR result, and 56 (88.9%) patients had their vancomycin order discontinued within 24 hours of the negative result. The mean total LOS was similar between groups. No differences were observed in clinical outcomes and adverse events between groups [31].

Other retrospective study aimed to evaluate the analytical performance of the MRSA/SA SSTI assay for rapid detection of MRSA in LRT specimens and its potential role in antimicrobial stewardship [32]. They prospectively analyzed in 100 respiratory specimens, from patients with VAP, the performance of the test. Xpert MRSA/SA identified MRSA in 5 of 6 specimens positive by standard-of-care culture, (sensitivity 83.3%). The false negative was a BAL specimen. Interestingly, Xpert MRSA/SA de-

Table 3 Potential implications of rapid diagnostic tests on the HAP/VAP empirical treatment

Author	Study type	Aim	Population	Assay	Result
Pham SN et al.[31]	Single center, retrospective, quasi-experimental (Pre-PCR vs PCR) study, in United States	To evaluate the impact of a pharmacist-initiated MRSA nasal PCR protocol on pneumonia therapy	210 patients: 138 Pre-PCR and 72 PCR, mainly in HAP	MRSA nasal PCR test	Compared with the Pre-PCR group, mean duration of IV vancomycin in the PCR group was 1.1 days shorter (2.5 ± 1.3 days vs 1.4 ± 1.2 days, P < .001). The median number of doses of IV vancomycin in the Pre-PCR group was 3 doses (IQR: 2-4) versus 1 dose (IQR: 1-2) in the PCR group (P < .001).
Trevino SE et al[32]	Single center, retrospective, in United States	To evaluate the analytical performance of the MRSA/SA SSTI assay for the rapid detection of MRSA in LRT specimens and its potential role in antimicrobial stewardship	100 specimens from VAP	GeneXpert® MRSA/SA	Potential reduction of free antibiotic days by 68.4% for vancomycin and by 83% for linezolid
Monard C et al.[22]	Observational and Retrospective Multicenter	Number of pneumonia episodes in which PCR-guided therapy differed form empirical therapy.	150 pneumonia episodes (CAP = 54, HAP = 68, VAP = 37)	BioFireFilmArray® Pneumonia plus Panel	Proportion of potential antibiotic modifications in VAP 87%, in HAP 79%
Buchan BW et al.[33]	Observational in 8 US clinical centers	To examine the potential impact of the BioFire® FilmArray Pneumonia Panel Test on antibiotic utilization.	259 samples BAL (n=237) or mini-BAL (n=22) from HAP and VAP	BioFire® FilmArray Pneumonia Panel test	Potential adjustment in 70,7% of patients, including discontinuation or de-escalation in 48,2%.
Peiffer-Smadja N et al.[34]	Prospective in 3 ICUs of one French academic hospital	We assessed the performance and the potential impact of the M-PCR on the antibiotic therapy of ICU patients.	95 clinical samples from 85 HAP or VAP patients (72 BAL and 23 PTC)	Unyvero Hospitalized Pneumonia (HPN, Curetis)	Expert panel: the RT-mPCR could have led to antibiotic changes in 66% episodes. Earlier initiation of an effective antibiotic: 21%, early de-escalation: 39%, and optimization: 3%. Among 17 empirical treatments with carbapenems, 10 could have been de-escalated
Pickens C et al.[35]	Retrospective in 4 hospitals of United States	To predict the impact of Unyvero LRT Panel results on adjustment of empiric antibiotic regimens.	659 hospitalized patients with LRTI	Unyvero Lower Respiratory Tract Panel	The LRT Panel result predicted no change in antibiotics in only 12.4%. In 65.9% of patients the results favored de-escalation (69% had unnecessary MRSA coverage and 64% had unnecessary P aeruginosa coverage).
Posteraro B et al.[36]	Prospective in a large university hospital in Italy	Changes to targeted and/or appropriate antimicrobial therapy	212 respiratory samples from 150 COVID-19 patients mechanically ventilated HAP, VAP	FilmArray® Pneumonia plus Panel	Panel results allowed initiating or changing organism-targeted antibiotics in 118 (98.3%) of 120 episodes

LRTI: lower respiratory tract infection. CAP: community acquired pneumonia. HAP: hospital acquired pneumonia. VAP: ventilator associated pneumonia. LOS: length of stay. IV: Intravenous. POCT: point-of-care test. RT-PCR: real-time polymerase chain reaction. ICU: Intensive Care Unit. SOC = Standard of care. BAL: bronchoalveolar lavage TA: tracheal aspirate, BW: bronchial washing. PTC: plugged telescoping catheter. IQR: interquartile range

tected MRSA in five specimens where MRSA was not recovered by routine culture: specificity 94.7%, PPV 50%, and NPV 98.9%. In order to study the potential impact of this findings on the antibiotic use, the clinical data of the patients were obtained from clinical data repository, including microbiological culture results as well as antimicrobials consumption. They found that 96 patients received vancomycin and/or linezolid. Those four subjects who did not receive these agents were negative for MRSA based on both Xpert MRSA/SA and culture. If the anti-MRSA agent had been discontinued one calendar day after a negative RDT result in patients without any additional culture or PCR results positive for MRSA (including surveillance swabs), the vancomycin total antibiotic-days would have decreased by 68.4% (512 days) to a mean duration of 2.7 days, and linezolid by 83% (253 days) to a mean duration of 1.9 days.

In the aforementioned retrospective study of 150 pneumonia episodes (54 CAP, 68 HAP and 37 VAP) an expert committee considered that in HAP cases antibiotics should have been de-escalated 37% and escalated 27% of the times, while in VAP even 49% might have been de-escalated and 24% should have been escalated according to the RDT results [22]. Of course, it is a retrospective study and the clinical impact of having prescribed the antibiotic according with the RDT results is unknown but is shows that it could be a very useful complementary tool for saving antibiotics.

The potential impact of the BioFire® FilmArray® Pneumonia Panel Test on antibiotic utilization has also been studied in 259 BAL samples from patients with HAP/VAP [33]. This RDT showed 96.2% positive agreement and 98.1% negative agreement for the qualitative identification of 15 bacterial targets compared to standard bacterial culture. Viral targets were identified by this RDT in 17.7% of specimens tested, of which 39.1% were detected in conjunction with a bacterial target. A review of patient medical records, including clinically prescribed antibiotics, revealed the potential for antibiotic adjustment in 70.7% of patients based on the RDT result, including discontinuation or de-escalation in 48.2% of patients, producing an average saving of 6.2 antibiotic days/ patient. It is worth noting that molecular tests for viral pathogens were clinically ordered for only 93/259 (35.9%) BAL samples submitted for bacterial culture and included primarily multiplexed respiratory panel tests. At least one viral target was detected by the RDT in 46/259 (17.7%) BAL specimens, either alone or in addition to bacterial targets. Only 11/46 (23.9%) specimens with a positive viral detection by the RDT had a clinician-ordered molecular test for viral pathogens. Although the role of viral pathogens is not well stablished in HAP/VAP, there were 7 BAL specimens positive for influenza A/B virus. Early identification of these agents might have led to prescribe specific antivirals that could have shortened the duration or severity of the episode.

Another study tested the usefulness of the Unyvero Hospitalized Pneumonia (HPN, Curetis) platform for potential optimization of broad-spectrum antibiotics in 95 clinical samples from 85 ventilated HAP or VAP patients [34]. This panel is another RDT able to detect 21 bacteria and 19 resistance genes on respiratory samples within 5 hours. A total of 90/112 bacteria were detected by this RDT with a sensitivity of 80% and specificity of 99%. The sensitivity was better for Gram-negative bacteria (90%) than for Gram-positive cocci (62%). There were 14 bacteria detected by this RDT that were not found in conventional cultures and 5/8 ESBL (CTX-M gene) and 4/4 carbapenemases genes (3 NDM, one oxa-48) were also identified. This RDT could have led to the earlier initiation of an effective antibiotic in 20/95 patients (21%) and to early de-escalation in 37 patients (39%) but could also have led to one (1%) inadequate antimicrobial therapy. Among 17 empiric antibiotic treatments with carbapenems, 10 could have been de-escalated in the following hours according to the RDT results. This RDT also identified 2 unexpected cases of severe legionellosis confirmed by culture methods. This study is another example of how RDT could make an impact in a better adequacy of antimicrobials.

This very RDT was used in another retrospective study on 659 hospitalized patients for microbiological diagnosis of suspected pneumonia [35]. Similar results to the previous study were found with an overall sensitivity of 85.7%, specificity of 98.4% and a NPV of 97.9%. According with the RDT result only 12.4% of cases did not need a change in prescribed antibiotics. Reassured by the excellent NPV of this RDT panel, the authors determined that if MRSA or P. aeruginosa were not detected by the panel, then anti-MRSA and/or anti-pseudomonal therapies were not indicated. Accordingly, antibiotic de-escalation was recommended in 65.9% (405/615) of patients, of whom 278/405 (69%) had unnecessary MRSA coverage and 259/405 (64%) had unnecessary *P. aeruginosa* coverage.

Finally, it is worth mentioning a prospective study performed in 150 COVID-19 patients mechanically ventilated with the Film Array Pneumonia Plus panel. A total of 212 samples were processed for standard culture and tested with the RDT from 150 patients suspected of bacterial pneumonia. The RDT results were immediately accessible to ICU clinicians for antimicrobial therapy management. Etiologically, 120 samples were positive and 90 were negative by both methods. RDT detected no culture-growing organisms (mostly *S. aureus* or *P. aeruginosa*) in 19 of 120 samples or antimicrobial resistance genes in two culture-negative samples for *S. aureus*. Fifty-nine (27.8%) of 212 samples were from empirically treated patients. Antibiotics were discontinued in 5 (33.3%) of 15 patients with RDT negative samples and were escalated/deescalated in 39 (88.6%) of 44 patients with RDT positive samples. Overall, antibiotics were initiated in 87 (72.5%) of 120 pneumonia episodes and were not administered in 80 (87.0%) of 92 no-pneumonia episodes. Antimicrobial-resistant organisms caused 78 (60.0%) of 120 episodes. Authors concluded that RDT in LRT samples may become indispensable for the clinical and therapeutic management of VAP or non-VAP episodes in ICU patients with COVID-19.

CONCLUSIONS

In agreement with the public policy document that the Infectious Diseases Society of America (IDSA) published a few years ago, declaring that, in order for tests to have a positive

impact on patient care, new tests need to provide information about the causative organism, including antimicrobial susceptibility/resistance information, if possible, and must have rapid results, ideally within 1 h [37], we have seen how these RDT are now a real useful tool, complementary to clinical judgment in the treatment of LRTI. In the difficult decision-making process of treating a critical patient with CAP/HAP/VAP accurately and promptly, the classic strategy based on risk factors is no longer justified because it leads to the excessive use of broad-spectrum antibiotics while potential pathogens are undetected. A great educational effort must be made among intensivists and microbiologists to implement these new rapid diagnostic tests into clinical practice because the positive impact on patient care can only be achieved if physicians act quickly upon the results and start adequate or stop inadequate antibiotics in these critically ill patients with little room to fail.

It is highly important to know very well the limitations of the particular RDT that is being used because those microorganisms or mechanisms of resistance not included in the RDT cannot be ruled out.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Value of syndromic panels in the management of severe community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia requiring hospital admission is a prevalent and potentially serious infection, especially in high-risk patients (e.g., those requiring ICU admission or immunocompromised). International guidelines recommend early aetiological diagnosis to improve prognosis and reduce mortality. Syndromic panels that detect causative pathogens by molecular methods are here to stay. They are highly sensitive and specific for detecting the targets included in the test. A growing number of studies measuring their clinical impact have observed increased treatment appropriateness and decreased turnaround time to aetiological diagnosis, need for admission, length of hospital stay, days of isolation, adverse effects of medication and hospital costs. Its use is recommended a) per a pre-established protocol on making the diagnosis and managing the patient, b) together with an antimicrobial stewardship programme involving both the Microbiology Service and the clinicians responsible for the patient, and c) the final evaluation of the whole process. However, we recall that microbiological diagnosis with traditional methods remains mandatory due to the possibility that the aetiological agent is not included among the molecular targets and to determine the antimicrobial susceptibility of the pathogens detected.

Key words: molecular diagnostic techniques, rapid diagnosis, high-throughput nucleotide sequencing / methods, respiratory tract infections, pneumonia / diagnosis, pneumonia / microbiology

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INTRODUCTION

According to recent data from the World Health Organisation, lower respiratory tract infections, including pneumonia, are the third leading cause of death worldwide and are the most deadly infectious diseases.

Aetiological diagnosis is a challenge due to the difficulty in obtaining representative samples of the lower respiratory tract, except in intubated patients, and the low positivity of blood cultures.

Appropriate early antimicrobial treatment is essential to reduce mortality and improve patient outcomes.

Syndromic diagnostic panels that allow the detection of multiple microbial targets with short turnaround times have been available in recent years. In this brief review, we update the available evidence on their use.

CURRENT EPIDEMIOLOGY AND AETIOLOGY OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA REQUIRING HOSPITAL ADMISSION

The severity of pneumonia ranges from mild to severe and is particularly dangerous in patients at the extremes of age, those with comorbidities (e.g., COPD) or immunocompromised.

Severe adult community-acquired pneumonia (CAP) is defined as pneumonia occurring in such patients who have not been hospitalised in the previous month.

CAP of moderate severity is usually treated in the inpatient ward (20-40% of cases) [1]. However, up to 1-10% of patients may require admission to an intensive care unit for management.

Several pathogens cause pneumonia, including viruses, bacteria and fungi. Traditionally, bacteria include *Streptococcus pneumoniae*, *Haemophilus influenzae* and atypical cases of pneumonia (e.g., *Chlamydophila pneumoniae*, *Mycoplasma*

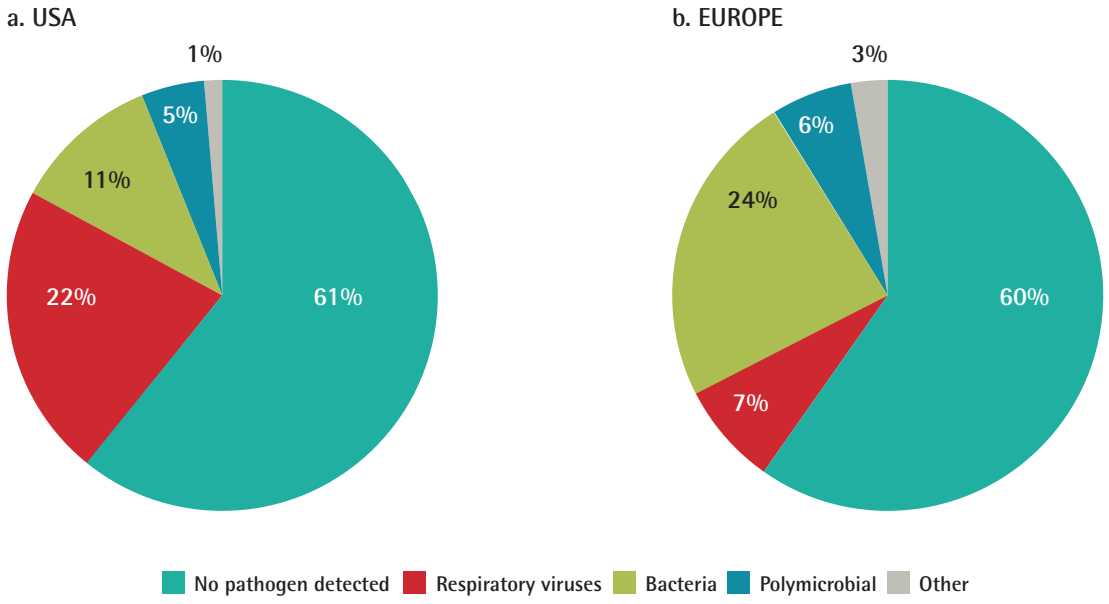

Figure 1 | **Aetiology of CAP in the USA and Europe**

pneumoniae, *Legionella* spp.). The most prevalent viruses are influenza A and B, respiratory syncytial virus (RSV), rhinoviruses, parainfluenza virus, and SARS-CoV-2. Less frequently, *Nocardia* spp. and mycobacteria are also found. The development of the disease largely depends on the host immune response, with pathogen characteristics having a less prominent role [2].

The prevalence of these pathogens varies between geographical regions. A recent study by Torres et al. shows these differences between Europe and the USA (Figure 1). In both cases, the aetiology was not discovered in up to 60% of patients. However, in Europe, bacteria predominate (24%), and, in the USA, respiratory viruses come in the first place (22%) [3]. Differences may be explained by the difficulty in obtaining valid respiratory samples to establish the diagnosis, antibiotics before sampling, and the sensitivity of diagnostic tests.

Modified from Torres et al. [3]. Aetiology of CAP in adults in the USA from 2010-2012 (2,488 cases). Aetiology of CAP in adults in Europe from 2003-2014 (3,854 cases).

Schlaberg et al. studied viral diagnosis in children hospitalised with CAP without a previously identified aetiology by next-generation sequencing (RNA-seq) and pan viral group PCR for 19 viral families. These techniques were able to identify additional viruses in one-third of the patients. Human bocavirus, Coxsackieviruses, human parainfluenza virus 4, and human rhinoviruses C and A were more commonly detected in children with CAP compared with control subjects, but only human bocavirus was more common than in control subjects (19%; aOR 9.1, CI 1.6-103). This suggests that these pathogens may have played an etiologic role in CAP.

We have briefly reviewed the aetiology of CAP to show that the pathogens responsible for CAP are still the commonly recognised ones. Furthermore, these microorganisms are the ones that should be included in syndromic diagnostic panels using molecular methods to identify most of the targets of clinical interest.

TRADITIONAL MICROBIOLOGICAL DIAGNOSIS OF PNEUMONIA

International guidelines recommend reaching an aetiological diagnosis [4,5]. In addition, the appropriateness of early antibiotic or antiviral treatment leads to a decrease in mortality in this entity [6].

From the point of view of the Microbiology Service, the traditional techniques for the diagnosis of conventional infections by typical pathogens (Gram stain and culture of good quality samples from the lower respiratory tract, with identification of the potential pathogen and performance of antibiogram tests) are not very sensitive and slow. Despite this, they continue to be used as the gold standard against which new and emerging diagnostic techniques are compared.

For viral infections, molecular techniques have taken over from older techniques (e.g. antigen detection, direct immunofluorescence, viral culture) and are considered the gold standard for diagnosing this group of microorganisms.

In addition to sputum sampling (for Gram stain and culture), blood cultures, urine for pneumococcal antigen and *Legionella* spp. detection, and nasopharyngeal exudate for SARS-

Table 1 Syndromic panels for the diagnosis of community-acquired respiratory infections

Diagnostic assay	Microorganisms detected	Type of sample	Turn-around-time
Verigene, Luminex	6 viruses 3 bacteria	Nasopharyngeal swab	<2h
NxTAG, Luminex	18 viruses 3 bacteria	NF, BAL, nasal aspirate, TA, sputum, FA	5-6 h
DiagCore,Quiagen	19 viruses 3 bacteria	All types of samples	1 h
Clart Pneumovir 2, Genomica	18 viruses	NF, nasopharyngeal lavage, BAL	2 h
Xpert Xpress SARS-CoV-2/Flu/RSV, Cepheid	4 viruses	NF, nasal exudate, nasal lavage/aspiration	36 min
ePlex Respiratory Pathogen 2, GenMark	16 viruses 2 bacteria	NF	90 min
Unyvero, Curetis	20 bacteria *P. jirovecii* 17 resistance markers	Sputum, TA, BAL	<5 h
Anyplex II RV16, Seegene	16 viruses	NF, nasopharyngeal aspirate, BAL	4,5 h
RespiFinder 2SMART, PathoFinder	20 viruses 4 bacteria	Sputum, BAL, NF, nasopharyngeal aspirate	2,5 h
bioFire FilmArray 2.0 Pneumonia plus, bioMerieux	18 bacteria 9 viruses 7 Resistance markers	Sputum, TA, BAL	<1 h
bioFire Respiratory Panel 2.1 Plus, bioMerieux	4 bacteria 19 viruses	NF	45 minutes

NF: nasopharyngeal exudate. TA: tracheal aspirate. FA: pharyngeal exudate. BAL: bronchoalveolar lavage

CoV-2 detection, are obtained in most patients with moderate CAP admitted to the internal medicine ward [7].

WHAT ARE THE SYNDROMIC PANELS FOR THE DIAGNOSIS OF THIS ENTITY? WHAT IS THEIR DIAGNOSTIC YIELD?

Several syndromic panels are available for the etiological diagnosis of CAP (https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests), which are summarised in Table 1. They differ in terms of the diagnostic technique used, the pathogens detected, the type of sample that can be used, the sample volume required, the time to results and the kind of result (e.g. qualitative or quantitative).

Challenges faced by these diagnostic panels include, among others, the prevalence of the aetiology for the choice of microorganisms included in the assay, the over-information that may occur for the prescribing doctor (e.g., risk of additional diagnostic studies and unnecessary treatments), interpretation of co-infection detection, the definition of the reference standard, rapid communication of results from the Microbiology Service (24/7), microbiological quality control of samples (e.g., prior Gram staining), use as point-of-care testing (POCT) outside the Microbiology Service and, finally, replacement or complement of other traditional diagnostic methods.

These assays have excellent diagnostic sensitivity and specificity [8-15]. The advantages of these syndromic panels lie in their ease of execution, the small sample volume required and the short time to result [16].

Disadvantages include that the panel composition is predefined, making it impossible to diagnose microorganisms not covered; diagnostic performance depends on the type of sample to be tested; some systems allow processing of individual samples, as they arrive in the laboratory, while others require batch testing; results are usually qualitative, except for Film Array®, which gives semi-quantitative results; it is not easy to differentiate between colonisation and infection by *S. pneumoniae* and *H. influenzae*; turn-around-time varies between commercial assays; and, finally, the cost of these tests is high and has a direct impact on the budget of the Microbiology Service.

WHAT IS THE AVAILABLE EVIDENCE ON THE IMPACT OF USING THESE PANELS?

Since its appearance on the market, scientific evidence has been generated about its impact on the different process and outcome indicators [17,18]. The former include time to optimisation of antibiotic treatment and duration of antibiotic therapy. The latter include the need for hospital admission, length of stay, clinical cure, readmission or 30-day mortality, adverse drug reactions and hospital costs.

Among the publications available, we have selected the following that we consider to be of interest. Rappo et al. studied the impact of rapid diagnosis of respiratory viruses in adults using BIORFIRE Respiratory Panel® compared to standard diagnosis by viral antigen detection [19]. The study is a retrospective quasi-experimental work in the 2010-11 (standard diagnosis) and 2012 (PCR diagnosis) seasons. They included 339 patients diagnosed with a viral infection. The use of PCR allowed for shorter turnaround time (1.7 h vs 7.7 h), fewer admissions (50% vs 61%, p=0.046), shorter length of stay (38.8 h vs 49.8 h, p=0.040), shorter duration of antibiotic administration (23.7 h vs 48.1 h, p=0.032) and ordering fewer chest X-rays in this population (p=0.005). However, these differences did not hold when the diagnosis was of a respiratory virus other than influenza.

Rogers et al. found similar results in a subsequent study evaluating standard molecular diagnosis of influenza A/B in the 2011-12 season using BIO FIRE Respiratory Panel® in the following season (2012-13). This was a retrospective quasi-experimental study with 1136 children older than three months included, with a pneumonia prevalence of 32%. When using the syndromic panel, the authors found a shorter response time (6.4 h vs 18.7 h, p<0.001) and a higher number of patients diagnosed in the emergency department before admission (52% vs 13%, p<0.001). In terms of antibiotic use, there were no differences in the indication for antibiotic use. Still, when the result was received in less than four h, the duration of antibiotic treatment was shorter (p<0.003). Furthermore, in patients with a positive result, hospital stay and respiratory isolation duration were shorter (p=0.03 in both cases).

In a pragmatic, open-label, randomised controlled trial, Brendish et al. included 714 adult patients within 24 h or presenting to the emergency department with acute respiratory illness of fever over two winter seasons [20]. The routine use of molecular POCT for respiratory viruses did not reduce the proportion of patients treated with antibiotics significantly. However, many patients were started on antibiotics before the results of POCT could be made available. Despite this, more patients in the POCT group received single doses or brief antibiotics courses than patients in the control group (17% vs 9%, p=0.0047). POCT was also associated with a reduced length of stay (5.7 d vs 6.8 d, p=0.0443) and improved the use of antivirals against influenza (91% vs 65%, p=0.0026) and was safe. We found equivalent results in other papers [21-23], some even with decreased hospital costs [22,24].

The impact of the BioFire FilmArray Pneumonia® panel on 259 BAL samples from adult inpatients was evaluated by Buchan et al. [14]. The use of this assay resulted in a 63.3% increase in specimens reported as positive. Over 99% of culture-negative discordant results were positive using an alternative molecular test or were below the culture threshold for reporting, suggesting that these were not false-positive detections. A review of patient medical records revealed the potential for antibiotic adjustment in 70.7% of patients, including discontinuation or de-escalation in 48.2% of patients, resulting in an average savings of 6.2 antibiotic days/patient.

This increase in the number of aetiological diagnoses has also been highlighted in other works, with adjustment of antibiotic treatment in a high number of patients and increased de-escalation [15].

The above mentioned studies were carried out before the COVID-19 pandemic. In a more recent work, Barrasa et al. studied the prevalence of co-infections and secondary infections in COVID-19 patients using traditional cultures and the BIOFIRE® FILMARRAY® Pneumonia Panel plus (FA-RP). They included 92 consecutive adult patients admitted to the ICU at the Araba University Hospital in Vitoria-Gasteiz (Spain) with the diagnosis of severe pneumonia caused by SARS-CoV-2 between March 4th - June 2nd 2020 (first wave) [25]. In 63 patients, BAL or tracheal aspirates were collected for microbiologic culture, and in 33 (52%), the BioFire panel was also used (turn-around-time of about 67 min). None of the 33 FA-RP tests (14 performed on admission) identified other respiratory viruses. At admission or in the first 48 h of ICU stay, 32 microbial isolates were found in 24 patients (co-infections, 26%, 24/92). In these patients, concordant results between the FA-RP (≥ 10^4 DNA copies/ml) and cultures (BAL with a cut-off of 10^4 CFU/ml) were obtained in 11 of 14 patients (overall agreement = 78%, kappa = 0.59 [95% CI 0.21–0.96]). Discordant results were obtained in three samples (*Moraxella catarrhalis, Proteus* spp and *Streptococcus agalactiae*). Conversely, 125 microbial isolates were found in 43 patients (secondary infections, 47%, 43/92) during ICU admission. Most samples were respiratory (52%), followed by urine (22%), blood (18%) and catheter tips (8%). The most commonly isolated microorganisms were *P. aeruginosa, E. faecium* and *Enterobacterales*, which represented half of the isolates in all secondary infections. Concordant results between the FA-RP and cultures were obtained in 12 out 19 patients (overall agreement = 63%, kappa = 0.31 [95% CI -0.05–0.67]), and discordant results were obtained in 6 samples, *Enterococcus faecalis* [2], *Aspergillus fumigatus* [2], *Enterococcus faecium* [1] and *Candida albicans* [1], targets not included in the panel. These results point to the need for microbiological diagnosis using real-time PCR and traditional cultures.

In summary, the use of syndromic multiplex polymerase chain reaction testing, coupled with antimicrobial stewardship, increases the timeliness of antiviral prescription in influenza patients and the rapid appropriateness of antibiotic treatment.

It is recommended to implement these systems together with the education of prescribing physicians.

The use of a pre-established diagnostic and management algorithm is recommended for the most significant clinical benefit. And monitoring end-user compliance with the algorithm to optimise patient management protocols.

These systems have been shown to support decision making (joint assessment of results and other diagnostic tests - e.g. procalcitonin).

These results justify the need for Clinical Microbiology Services to work 24-h a day, 7 days a week (24/7) [12,26-32].

WHAT ARE THE CURRENT RECOMMENDATIONS FOR THEIR USE

The use of syndromic pneumonia panels is recommended in symptomatic patients, those with new or worsening radiographic infiltrates, moderate to severe pneumonia, previous empirical antibiotic treatment, when there is concern about the presence of multi-resistant microorganisms or co-infections, for the detection of both bacteria and viruses (e.g., if viruses are not underdiagnosed), or in patients with certain diagnostic needs (e.g., immunocompromised patients) [2,5,18]. Currently, molecular diagnostics is the gold standard for the diagnosis of viral respiratory infections [5,33,34].

The 2019 American Thoracic Society guideline recommends [4]:

a) Do not obtain sputum for Gram stain and culture in patients with CAP who are not admitted (strong recommendation with a low level of evidence).

b) Perform etiological diagnosis in patients with CAP who are admitted, especially if they require mechanical ventilation, and with risk factors for MDR (e.g. MRSA, *Pseudomonas aeruginosa*) (strong recommendation with a very low level of evidence).

In an excellent review by Cilloniz, Torres et al., the authors propose to use them in patients with CAP with clinical suspicion of influenza or *P. aeruginosa*, or severe CAP requiring ICU admission [1]. And in all patients with clinical suspicion of hospital- and ventilator-associated pneumonia.

CONCLUSIONS

In patients with respiratory infections requiring hospitalisation, syndromic panels have been shown to increase aetiological diagnosis due to their higher sensitivity, shorten the turnaround time, decrease the duration of antibiotic treatment and increase the use of antivirals against influenza, shorten time to respiratory isolation of the patient and days of isolation, allow for de-escalation of antibiotics, and reduce the cost of antibiotic treatment and hospitalisation. It is recommended to use them in conjunction with an antimicrobial stewardship programme and a predetermined management algorithm.

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Usefulness of thoracic ultrasound for diagnosis and follow-up of pneumonia

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ABSTRACT

Classically the diagnosis of both bacterial and viral pneumonias was made with chest radiology, later the use of chest CT was implemented, however in recent years lung ultrasound has become very important in the diagnosis of pulmonary pathology and increased in pandemic by SARS-CoV-2, due to the practicality of being done at the patient's bedside, the ability to be reproducible, and the decrease in radiation exposure to patients

Keywords: pneumonia, ultrasound, lung, ultrasonography.

INTRODUCTION

Pneumonia is a common respiratory infection in adults and children with high morbidity and mortality. It can have a bacterial origin, usually *Streptococcus pneumoniae* and/or viral as we have seen in the last two years by SARS-CoV-2, which pathophysiologically affects the pulmonary alveolus causing consolidations in it and decreasing gas exchange [1].

At the beginning of medicine, the diagnosis of infection was a challenge only with physical examination, later with the passage of time and the development of Thoracic Radiology there was an improvement in it, then the arrival of tomography increased the sensitivity of the diagnosis this being the gold standard, but as limitations it has the increase in the level of radiation to the patient and the high cost, in addition to the difficulty of performing it in critical patients [2].

Recently, pulmonary ultrasound has shown to be very useful in a series of pulmonary pathologies. In fact, lung ultrasound is more sensitive for diagnosing pleural effusion than chest radiography. In addition, other studies have shown its use as a diagnostic method for pneumonia with positive results. significant. It has the advantage of portability, simplicity, rapidity, and similar sensitivity and specificity compared with CT [3].

Several studies and meta-analyses have been carried out comparing lung ultrasound vs. chest X-ray and tomography with significant results, due to which ultrasound has become more relevant in the last decades for the diagnosis of this pathology [3].

USEFULNESS OF THE DIAGNOSIS OF PNEUMONIA BY LUNG ULTRASOUND

One of the current diagnostic tools for pneumonia is lung ultrasound, on which numerous studies have been carried out in recent years regarding its usefulness in the diagnosis, prognosis and follow-up of patients with pneumonia [4].

According to Reissig and Copetti's study the most important parenchymal criterion for the diagnosis of community-acquired pneumonia (CAP) is the presence of air bronchogram within a hypoechoic area, which can be found in about 70-97% of cases, while among the pleural criteria, pleural effusion was the most frequent factor to be found (in about 34-61% of cases). Determination of vascularisation is very useful, especially for differential diagnosis [5].

One of the features found in the diagnosis of CAP are B-lines (Figure 1), although they are not a specific finding. These are lines perpendicular to the pleural line and parallel to each other. They are usually caused by decreased alveolar aeration and fluid accumulation under the visceral pleural, thickening of interlobular septa, mostly related to interstitial occupation [4].

In general, B-lines are diffusely distributed in patients with cardiogenic pulmonary oedema, acute respiratory distress syndrome (ARDS) and interstitial lung diseases. In patients with pneumonic consolidation, B-lines are often seen focally, multifocally or patchily in ground-glass opacities or around areas of consolidation [4].

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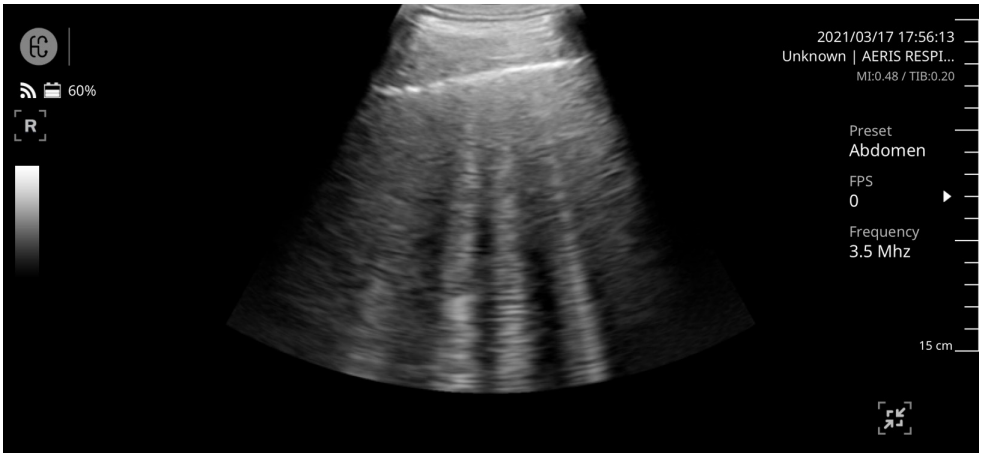

Figure 1 | **Pneumonia due to COVID-19. Thoracic ultrasound where multiple B lines are seen leaving the pleural line very typical of COVID-19 pneumonia**

In interstitial pneumonia, an interstitial ultrasound pattern combined with preserved areas is strongly suggestive of viral pneumonia and correlates with CT findings [4,6].

Other findings that can be found in the ultrasound diagnosis of pneumonia include ultrasound consolidation (Figure 2), which is defined as a predominantly subpleural hypoechoic region or a hypoechoic region with liver-like density. Differential diagnoses include pneumonia, pulmonary infarction, tumours, metastases and atelectasis. Consolidations corresponding to pneumonia usually have irregular, non-rounded borders. In the presence of subpleural consolidations, the pleural line is not clearly evident and pleural sliding is decreased or absent. Consolidations may include air bronchograms (hyperechogenic tree-like images corresponding to air-filled bronchi), not specific to pneumonia, but useful to distinguish it from obstructive atelectasis, which has no air bronchogram [4].

In patients with pneumonia, interstitial lung disease and ARDS, the pleural linings can be seen to be thickened and serrated. Several studies have shown that pleural effusion is detected by lung ultrasound (LUS) in 30-46% of patients with pneumonia [4].

Several studies have analysed the sensitivity and specificity of LUS in the diagnosis of pneumonia, such as the study by Reissig et al, in which the sensitivity of LUS for detecting CAP varies between 93.4 and 98%, and the specificity between 97.7 and 95% [5].

In the prospective multicentre study by Javaudin et al, including emergency department patients with a presumptive diagnosis of CAP, we found that LUS modified the probability of CAP diagnosis in 72% of cases, mostly (77%) according to the probability of the adjudication committee. The main finding was that LUS reduced diagnostic uncertainty from 73% to 14% [7].

Other studies have assessed the usefulness of LUS compared to other diagnostic techniques such as chest radiography (CXR) or chest computerized tomography (CT) [4].

The systematic review-meta-analysis by Hansell et al, aimed to evaluate the diagnostic accuracy of LUS compared to CXR and auscultation versus CT for pleural effusion, lung consolidation and collapse in mechanically ventilated intensive care patients. They found that LUS had a higher overall sensitivity and specificity for detecting pleural effusion and lung consolidation than CXR. In pleural effusion and lung consolidation/collapse, pooled analyses of the diagnostic accuracy of LUS showed that sensitivity ranged from 91-92%, the area under the SROC curve (AUC) was 0.96 and the diagnostic OR ranged from 134-160. The DOR and AUC for LUS suggest excellent diagnostic accuracy. LUS is more appropriate than CXR for detecting pleural effusion and pulmonary consolidation [8].

In the meta-analysis by Long L. et al, LUS was shown to have a high sensitivity 88 % (95 % CI 0.86-0.90) and specificity 86 % (95 % CI 0.83-0.88) for the detection of pneumonia in adults compared to chest radiography or chest CT [3].

Two other papers discussed in the study by Long et al show results according to the results obtained, one is the study by Bourcier in 2014, which revealed a significantly higher sensitivity of LUS for the diagnosis of acute pneumonia compared to chest radiography (95 % vs. 60 %, $P<0.05$). Furthermore, when chest CT was performed due to a difficult diagnosis, the efficiency of LUS in the diagnosis of acute pneumonia was 100 % [3]. The other study is a meta-analysis carried out by Chavez et al, which found that that the pooled sensitivity and specificity for the diagnosis of pneumonia by LUS were 94% (95% CI, 92%-96%) and 96% (94%-97%), respectively [3].

For coronavirus pneumonia, many studies have been reported that support the use of LUS for diagnosis, describing the most frequent findings and their distribution [9].

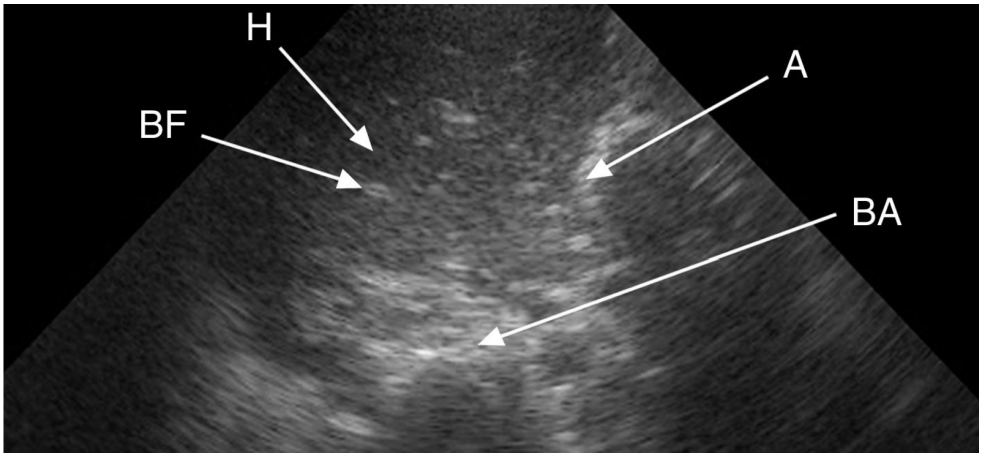

Figure 2 | **Bacterial pneumonia consolidation. Thoracic ultrasound with convex probe showing typical findings of bacterial pneumonia**

H: hepatization; A: atelectasis; BF, fluid bronchogram; BA: aerial bronchogram

Castelao et al. described, based on a study of LUS, that the lower lobes and posterior regions had a greater tendency to be involved. LUS findings in COVID-19 pneumonia are similar to those described in patients with pneumonia before the COVID-19 era [4,10].

Mohamed et al. reported in an SR/MA the pooled proportion of multiple B-lines (including focal, multifocal and coalescent types) detected by LUS was 0.97 (95% CI 0.94-1.00), pleural line abnormalities was 0.70 (95% CI 0.13-1.00), small or large subpleural consolidation was 0.39 (95% CI 0.21-0.58), and pleural effusion was 0.14 (95% CI 0.00-0.37). The presence of multiple B-lines, focally, multifocally and coalescing, were the most common and consistent findings [11].

Large lobar or multilobar consolidations with air bronchograms are less common in the early stages of COVID-19 pneumonia. When larger consolidations are initially observed, bacterial pneumonia or bacterial overinfection should be suspected. Bigger consolidations may occur in later stages of COVID-19 pneumonia [4,9].

Volpicelli et al. classified ultrasound findings in conjunction with phenotypic patterns of patients to estimate the likelihood of deterioration in coronavirus pneumonia. In addition, they described an ultrasound sign associated with covid infection: the light beam (vertical band-like artefact that often appears and disappears from the screen with respiration). This is the early sonographic representation of interstitial involvement corresponding to the ground-glass opacities that are typically visible on CT studies in the lung periphery during early disease. The light beam is not specific for COVID-19 but should raise a high suspicion of COVID-19 lung involvement in its presence [12]

Peng et al. reported that lung ultrasound could provide comparable results with chest CT for the evaluation of COVID-19 pneumonia [6,9].

ULTRASOUND MONITORING AND FOLLOW-UP

In the initial phase of pneumonia, lung is diffusely echogenic, with an ultrasound appearance similar to liver, with irregular margins and hyperechogenic branching linear interior images corresponding to air bronchogram [13-15].

In more advanced stages, and after antibiotic treatment, the pneumonic consolidations show air images that translate progressive aeration of the pulmonary parenchyma. Another sign, also visible in CT, is liquid bronchogram, which consists of linear anechogenic images in the interior of the parenchyma. This sign, although not pathognomonic, should point to a central obstruction as the cause of consolidation [13-15].

Ultrasonography can also be able to distinguish between central neoplastic process and consolidated peripheral lung [13].

LUS is more sensitive than conventional radiography and even CT in the assessment of necrosis and abscessation in pneumonia [15]. In color Doppler ultrasound is possible to identify hypoechogenic areas that show hypoperfusion. Abscesses are visualized as nodular or oval images with well or poorly defined margins and a content that can be anechogenic or contain echoes and internal septa [13,14].

The importance of ultrasound in the evaluation of pneumonia is the detection of parapneumonic pleural effusion and intrapulmonary abscesses. In immunocompromised patients, ultrasound-guided aspiration has a special interest in order to obtain microbiological samples. It is useful in the monitoring of radiation-susceptible patients, such children and pregnant women, in emergency conditions, in airplanes, in rural regions, in resource-limited settings, in developing countries, in general doctors, and in immobilized patients in whom only one plane radiography can be performed [14,15].

The extent and severity of pulmonary infiltrates can be

numerically described with a reproducible and validated LUS score [15].

About COVID-19, the sensitivity, specificity and diagnostic accuracy of LUS have been reported to increase with the severity of COVID-19 pneumonia compared with chest CT scan [10].

According to several articles included in the study by Allinovi et al, LUS can detect the dynamical pulmonary changes associated with COVID-19 pneumonia. In the early phases, the main ultrasound finding is focal B-lines, while as the disease progresses, the B-lines become multifocal and confluent, with later development of clear consolidations. In convalescence, the B-lines and consolidations gradually disappear and are replaced by A-lines [10].

Ultrasound diagnosis of pneumonia and follow-up allow rapid therapeutic decisions [7].

CONCLUSION

Ultrasonography is useful in the diagnosis and follow-up of pneumonia and its complications; it can monitor the evolution of pneumonia even above chest X-ray with similar results to CT, and should therefore be included in diagnostic algorithms. It is a quick, innocuous and low-cost exploration, which does not require patient mobilization. Although it is apparently complex, after training and learning the different ultrasound patterns, it is a valuable tool for the study of thoracic diseases. It is important to work on learning and integrating this technique into the daily practice of pulmonologists, radiologists and emergency physicians.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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Ceftobiprole medocaril

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ABSTRACT

Ceftobiprole medocaril is a broad-spectrum 5th-generation cephalosporin with activity against Gram-positives such as methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*, and against Gram-negatives such as *Pseudomonas aeruginosa*. The recommended dose is 500 mg every 8 h in 2-hour infusions. Various clinical trials have demonstrated its usefulness in the treatment of community-acquired pneumonia and nosocomial pneumonia, with the exception of ventilator-associated pneumonia. In summary, it is a very useful antibiotic for the treatment of pneumonia.

Keywords: Ceftobiprole; antibiotic; multidrug-resistance; pneumonia

INTRODUCTION

One of the pandemics facing the world in the 21st century is that of superbugs and antimicrobial resistance. Infections by these superbugs could be responsible for millions of deaths in the coming decades. For this reason, the scientific community has been making a great effort for some time in the development of new antibiotics to face this great challenge. The result of this effort has been the appearance of new drugs, among which is ceftobiprole medocaril.

Pneumonia is the infection with the highest morbidity and mortality. It mainly impacts the extremes of life due to the special vulnerability during childhood and old age. Ceftobiprole medocaril is a new antibiotic for the treatment of pneumonia with a different antimicrobial profile than its predecessors.

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MICROBIOLOGICAL PROFILE

Ceftobiprole medocaril is a 5th generation cephalosporin (pyrrolidinone-3-ylidene-methyl cephalosporin) for parenteral use that has extended activity against Gram-negatives such as *Pseudomonas aeruginosa* or 85% of enterobacteria, and against Gram-positives such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and *Enterococcus faecalis*, among others. Ceftobiprole is generally not active against microorganisms that cause atypical pneumonia [1].

Ceftobiprole medocaril is capable of inhibiting cell growth through its binding to penicilling-binding proteins (PBPs), which hinders cell wall synthesis and induces bacterial death.

In relation to Gram-positives, its activity against MRSA is due to its union with the extended narrow groove of the PBP2a and its affinity to other staphylococcal PBPs (PBP1, PBP3 and PBP4). In the case of its activity against penicillin-resistant *S. pneumoniae*, it is mainly explained by its great affinity for PBP2b and PBP2x, unlike other beta-lactams such as ceftriaxone. Finally, its action against *E. faecalis* is due to its high affinity for enterococcal PBP [2].

Ceftobiprole is active against Gram-negatives such as *P. aeruginosa* and enterobacteria. It loses its efficacy against enterobacteria that express carbapenemases, Ambler's Class A β-lactamases such as extended spectrum β-lactamases (ESBLs), or AmpC β-lactamase types. It is active against *P. aeruginosa* due to its binding to PBP3 and loses its efficacy when it expresses metallo-carbapenemases (IMP and VIM) and D (OXA-10), carbapenemases or Ambler's Class A β-lactamases including ESBLs.

Finally, it is also active against some anaerobic bacteria such as *Clostridium* spp. and *Fusobacterium* spp. but not against others such as *Bacteroides* spp., *Prevotella* spp. and *Veillonella* spp.

Table 1 Main outcomes of randomized clinical trials of ceftobiprole in community-acquired pneumonia and hospital-acquired pneumonia.

CAP	Ceftobiprole	Ceftobiprole ± linezolid	95% CI of the difference
Clinical cure			
CE patients	200/231 (86.6)	208/238 (87.4)	-6.9, 5.3
ITT patients	240/314 (76.4)	257/324 (79.3)	-9.3, 3.6
Patients receiving i.v. therapy only	77/103 (74.8)	73/101 (72.3)	-9.6, 14.6
Switch to oral therapy	123/128 (96.1)	135/137 (98.5)	-6.4, 1.5
Microbiological eradication			
ME patients	60/68 (88.2)	69/76 (90.8)	-12.6, 7.5
Microbiological ITT	70/87 (80.5)	79/97 (81.4)	-12.4, 10.4
HAP	**Ceftobiprole**	**Ceftazidime/linezolid**	**95% CI of the difference**
Clinical cure			
CE patients	174/251 (69.3)	174/244 (71.3)	-10, 6.1
HAP (excluding VAP)	154/198 (77.8)	141/185 (76.2)	-6.9, 10
VAP	20/53 (37.7)	33/59 (55.9)	-36.4, 0
HAP (excluding VAP), mechanically ventilated	21/38 (55.3)	15/37 (40.5)	-7.6, 37.1
ITT patients	195/391 (49.9)	206/390 (52.8)	-10, 4.1
HAP (excluding VAP)	171/287 (59.6)	167/284 (58.8)	-7.3, 8.8
VAP	24/104 (23.1)	39/106 (36.8)	-26, -1.5
HAP (excluding VAP), mechanically ventilated	21/69 (30.4)	19/70 (27.1)	-11.8, 18.3
Microbiological eradication			
ME patients	87/162 (53.7)	106/170 (62.4)	-19.2, 1.9
HAP (excluding VAP)	73/116 (62.9)	81/120 (67.5)	-16.7, 7.6
VAP	14/46 (46)	25/50 (50)	-38.8, -0.4
Microbiological ITT	105/269 (39)	127/267 (47.6)	-16.9, -0.2
HAP (excluding VAP)	87/179 (48.6)	97/181 (53.6)	-15.3, 5.3
VAP	18/90 (20)	30/86 (34.9)	-27.9, -1.9

CAP, community-acquired pneumonia; CE, clinically evaluable; CI, confidence interval; HAP, hospital-acquired pneumonia; ITT, intention-to-treat; ME, microbiologically evaluable; VAP, ventilator-acquired pneumonia.

PHARMACOLOGICAL FEATURES

The recommended dose of ceftobiprole medocaril is 500 mg every 8 h in 2-hour infusions and is rapidly (<1 min) and almost completely converted to active ceftobiprole. The peaks of the active principle in the blood are reached 30 minutes after the start of the infusion. It has a low protein binding (approximately 16% and independent of concentration in the range of 0.5-100 mg/L) and a distribution volume of around 18-20/L [3].

At the recommended dose in subjects with normal renal function for a minimum inhibitory concentration (MIC) of 4 mg/L, the probability of achieving an MIC fT of 50% was 80%. Ceftobiprole is eliminated almost exclusively in the urine with about 88% of the administered dose recovered in urine. In patients with a creatinine clearance of 30-50 mL/min, it is recommended to space the dose every 12 hours. With creatinine clearance <30 mL/min, the dose will be reduced to 250 mg/12 h. Ceftobiprole has few drug interactions because it does not inhibit cytochrome P450 [4,5].

CLINICAL EXPERIENCE

There are two pivotal clinical studies of ceftobiprole medocaril conducted in 638 patients with community-acquired pneumonia and 781 patients with nosocomial pneumonia [6,7]. The first of them was performed in patients with CAP who required hospitalization. Patients were randomized 1:1 to ceftobiprole 500 mg every 8 h in 2-hour infusions versus ceftriaxone 2 g every 24 h in 30-minute infusions and stratified by pneumonia severity index (PSI). If there was suspicion of MRSA,

linezolid 600 mg every hour was associated in the ceftriaxone group and placebo in the ceftobiprole group. The primary endpoint was the clinical cure rate at the test of cure (TOC) visit (in both the ITT and CE populations). Secondary outcomes were microbiological eradication at TOC visit, clinical cure according to PSI, and pneumonia-specific mortality at 30 days. A total of 314 patients (ITT) were included in the ceftobiprole group and 324 in the ceftriaxone group, of which CE were 231 and 238, respectively. Regarding the main outcome, ceftobiprole treatment was found to be non-inferior to comparator treatment in both the ITT and CE populations (Table 1). In patients with PSI class IV-V, the cure rates also did not show differences (secondary outcome) between the ceftobiprole group and the comparator. Likewise, no differences were found according to microbiological etiology. In relation to microbiological eradication, the results were similar and no significant differences were observed (Table 1). Lastly, there were no deaths in the ceftobiprole group versus two in the ceftriaxone group. All this without notable security or tolerance problems.

The second study was conducted in patients with hospital-acquired pneumonia (HAP) [7]. In this case, patients were randomized 1:1 to ceftobiprole 500 mg every 8 h in 2-hour infusions versus ceftazidime 2 g every 8 h plus linezolid 600 mg every 12 h. A total of 781 patients were included, 391 in the ceftobiprole group (251 CE) and 390 in the ceftazidime/linezolid group (244 CE). The main outcome under study was again the clinical cure rate at the TOC visit (in both the ITT and CE populations). The main secondary outcome included microbiological eradication. Non-inferiority was demonstrated in the treatment of HAP with ceftobiprole versus ceftazidime/linezolid in both the CE and ITT populations (Table 1). However, this failed to demonstrate the non-inferiority of ceftobiprole in the subgroup of patients with ventilator-associated pneumonia (VAP). Very similar results were found for the secondary outcome, demonstrating non-inferiority for microbiological eradication of ceftobiprole with the exception of the VAP subgroup. There were no significant differences in mortality or safety and tolerability between the two treatment groups.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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Ceftaroline in severe community-acquired pneumonia

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ABSTRACT

Severe community-acquired pneumonia (SCAP) is associated with high mortality. Factor such as early adequate antibiotic therapy, delay in intensive care unit (ICU) care and pneumonia caused by resistant pathogens are associated with worse outcomes in SCAP patients. Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against Gram-positive pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA] and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative organisms. The efficacy and safety for the treatment of pneumonia was evaluated in three randomized control trials were ceftaroline demonstrated superiority against ceftriaxone for the treatment of pneumonia in hospitalized patients with Pneumonia Severity Index (PSI) III – IV.

Keywords: severe community-acquired pneumonia; *Streptococcus pneumoniae*; *Staphylococcus aureus*; ceftaroline

INTRODUCTION

Severe CAP is associated with high morbidity and mortality [1]. The early detection of severe pneumonia and the timely, adequate antimicrobial therapy are critical in managing these cases that affect in great proportion to elderly adults and patients with chronic comorbidities [1]. Based on this observation, early, adequate antimicrobial therapy could reduce mortality in severe CAP.

Due to the growing microbial resistance and continued need for appropriate antimicrobial coverage, newer antibiotics have been investigated in CAP, with an ability to cover the most frequent pathogens in pneumonia and their resistances. Ceftaroline is one of this new generation cephalosporins, has broad-spectrum in vitro activity against Gram-positive pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA] and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative pathogens. Ceftaroline is approved for their use in CAP in Europe and USA.

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MICROBIOLOGICAL PROFILE

Ceftaroline exhibits a greater binding affinity for penicillin-binding proteins (PBPs) and thus preventing the biosynthesis of the bacterial cell wall. Ceftaroline has high binding affinities to PBP 1- 3 and PBP-2A that mediates methicillin resistance in MRSA; and for PBP-1A, PBP-2A/B and PBP-2X that target *S. pneumoniae* including multidrug resistant strains.

Table 1 Antibacterial activity

Gram-positive bacteria	Gram-negative bacteria
Streptococcus pneumoniae	*Escherichia coli*
Staphylococcus aureus	*Klebsiella pneumoniae*
Methicillin-resistant *S. aureus* (MRSA)	*Haemophilus influenzae*
Methicillin-susceptible *S. aureus* (MSSA)	*Haemophilus parainfluenzae*
Vancomycin-intermediate *S. aureus* (VISA)	*Klebsiella oxytoca*
Vancomycin-resistant *S. aureus* (VRSA)	
Streptococcus pyogenes	*Morganella morganii*
Streptococcus agalactiae	*Moraxella catarrhalis*
Streptococcus anginosus group	
S. anginosus	
S. intermedius	
S. constellatus	

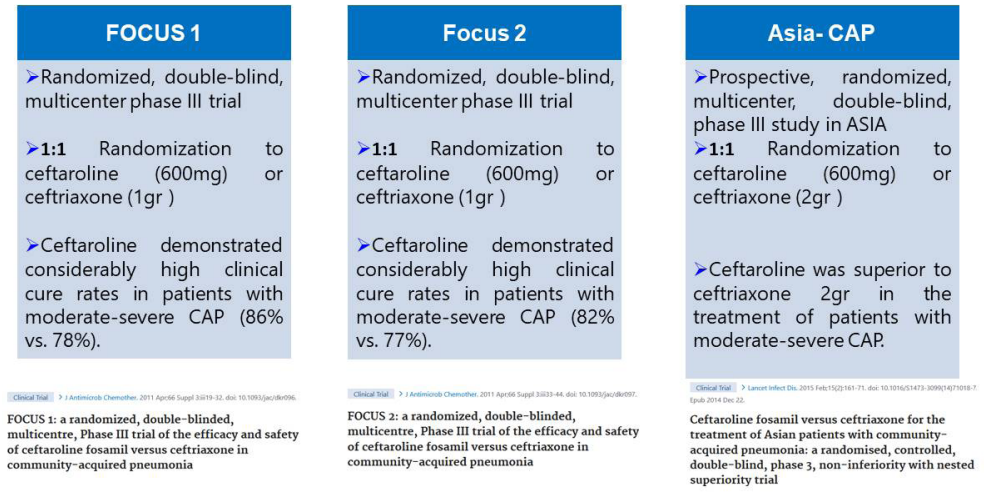

Figure 1 | **Ceftaroline fosamil: Clinical Experience**

Ceftaroline has demonstrated activity against a broad spectrum of gram-positive and gram-negative pathogens as show in table 1. However, ceftaroline does not have significant in vitro activity against extended-spectrum beta-lactamase (ESBL) producing microorganisms, AmpC-producing microorganisms, *Pseudomonas aeruginosa*, *Proteus* spp, *Prevotella* spp and *Bacteroide* spp.

PHARMACOLOGIC CHARACTERISTICS (PK/PD)

Ceftaroline is a time-depend antibiotic, whose best predictor of bacteriological and clinical efficacy is the percentage of time that the free drug concentration remains above the minimal inhibitory concentration (MIC) of the microorganism over the dosing interval (mean %f T >MIC). For the reduction of 2-log in bacterial load of *S. aureus* is 35%. In the case of *S. pneumoniae* the value required is 51%. With a dose of 600mg/12h infused over 60 minutes the probability of achieving these values for *S. aureus* and *S. pneumoniae* is >90% for the cut-off points established by EUCAST.

Plasma protein binding of ceftaroline is approximately 20% and terminal elimination half-life approximately 2.5 hours. Ceftaroline is primarily eliminated by the kidneys. The dose should be adjusted when creatinine clearance (CrCL) is ≤50 mL/min. The recommended durations of treatment are 5-7 days for CAP.

CLINICAL EXPERIENCE

The efficacy of ceftaroline in CAP was investigated in three double-blind, multinational, phase 3 trials (FOCUS 1 [2], FOCUS 2 [3] and Asian Trial [4]) in adult patients (aged>18 years) hospitalized with Pneumonia Severity Index (PSI) risk class III or IV (Figure 1). In the FOCUS 1 and 2 trials a dosage of 1gr of ceftriaxone was given, whereas in the Asian trial 2 gr of ceftriaxone was given. CAP cases causes by pathogens resistant to ceftriaxone were excluded (including MRSA).

The objective in all trials was determination of the non-inferiority of ceftaroline to ceftriaxone in terms of the clinical cure (defined as resolution of all signs and symptoms of pneumonia or improvement such that no further antimicrobial therapy was necessary) rate at the test of cure (TOC) visit in the modified intent-to-treat (MITTE) and clinically evaluable (CE) population.

Ceftaroline was well tolerated in all the trials and demonstrated non-inferiority to ceftriaxone in the MITTE and CE populations for the primary end point of clinical cure at the TOC visit (8–15 days after end of therapy).

In the integrated analysis, of the CE patients treated with ceftaroline, 84% achieved clinical cure, compared with 78% of ceftriaxone-treated patients. Clinical cure rates in the MITTE population were 83% versus 77% for ceftaroline and ceftriaxone. Ceftaroline and ceftriaxone were well tolerated; rates of adverse events, serious adverse events, deaths, and premature discontinuations caused by an adverse event were similar in both treatment groups [5].

In a meta-analysis of three trials including 1916 CAP patients, ceftaroline (600mg/8h) was superior to ceftriaxone (1–2 g /24 h) for 5–7 days in the MITT population (OR: 1.66; 95% CI 1.34, 2.06; $P < 0.001$) and in the CE (OR: 1.65; 95% CI 1.26, 2.16; $P < 0.001$) populations [6].

A subsequent analysis quantify the time to a clinical response, a proxy for the time to discharge readiness, among CAP patients including in the FOCUS 1 and FOCUS 2 trials. The results of the study showed that patients who received Ceftaroline were found to have shorter overall times to a clinical response and clinical stability relative to patients who received ceftriaxone [7].

The current ATS/IDA guidelines [8] and the update of the SEPAR guidelines [9] for the management of CAP patients incorporate ceftaroline as one of the ß-lactams recommended for the treatment of hospitalized patients with CAP.

Recently, our group published a case-control study were ceftaroline was mainly prescribed in cases with severe pneumonia (67% vs. 56%, p0.215) with high suspicion of *S. aureus* infection (9% vs. 0%, p 0.026). Patients who received ceftaroline had a longer length of hospital stay (13 days vs. 10 days, p0.007), while an increased risk of in-hospital mortality was observed in the patients who received ceftriaxone compared to the patients in the ceftaroline group (13% vs. 21%, HR 0.41; 95% CI 0.18 to 0.62, p 0.003). This study reported that the use of ceftaroline in hospitalized patients with severe CAP was associated with a decreased risk of in-hospital mortality [10].

The great bactericidal activity of ceftaroline against *S. pneumoniae* and *S. aureus*, makes it an excellent therapeutic option in the treatment of cases of severe CAP.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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ABSTRACT

Cefiderocol is a new siderophore cephalosporin with potent in vitro activity against gram-negative bacilli including *Enterobacterales* that produce all kinds of carbapenemases and non-fermenting Gram-negative with difficult-to-treat resistance. As a β-lactam, its efficacy is optimized in extended-perfusion and requires dose adjustment in renal dysfunction and hyperclearance. Its efficacy has been validated in three clinical trials, one of them in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. The clinical trial aimed at difficult-to-treat gram-negatives achieved the clinical and microbiological target, but the increase in mortality observed in the cefiderocol arm makes it necessary to demonstrate efficacy in real clinical practice. Cefiderocol is a good option among the new β-lactams for the treatment of pneumonia caused by Gram-negative bacilli carbapenem-resistant.

Keywords: Cefiderocol. Multiresistant bacterias. Carbapenemase. Difficult-to-treat resistance. *Acinetobacter baumannii*.

INTRODUCTION

In recent years, new β-lactam antibiotics have become available to us, essential for the treatment of infections by multi-drug resistant (MDR) Gram-negative bacteria. Cefiderocol is a novel siderophore cephalosporin, its main advantage lies in the breadth of its spectrum which includes Gram-negatives bacilli with difficult-to-treat resistance (DTR) and therapeutic gaps to be fulfilled, for instance carbapenem resistant as carbapenemase-metallo-β-lactamases producing Gram-negative bacilli, *Stenotrophomonas maltophilia*, carbapenem-resistant *Acinetobacter baumannii* and other non-fermenting MDR-bacilli with limited therapeutic choices.

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Cefiderocol shares a chemical structure in the C-7 side chain with ceftazidime and in the C-3 side chain with cefepime, which gives it a profile for Gram-negative bacilli and stability against β-lactamases [1], although its main distinguishing feature is its chlorocatechol side chain that chelates ferric iron. Cefiderocol, in addition to its entry into bacteria through porin channels like other cephalosporins, it's binding to iron allows to easily enter through active iron transport system [1], reaching high concentrations in the periplasmic space and thus exceeding most of the bacterial resistance mechanisms, such as efflux pumps, porins and ß-lactamases. Once inside the cell binding to BPB-3 and PBP-2 of cellular wall, leading to cell death (Figure 1) [1,2].

MICROBIOLOGICAL PROFILE

Cefiderocol shows potent in vitro activity against Gram-negative pathogens, including *Enterobacterales* and MDR carbapenem-resistant non-fermenters, almost no activity against Gram-positive cocci and anaerobes organism [2].

To assess the susceptibility of cefiderocol, numerous studies have been conducted since 2014 in the SIDERO-WT [3] program, in which clinical samples of Gram-negative MDR Gram-negative bacilli from all over the world have been tested, comparing the in vitro activity of cefiderocol against other antibiotics including the newer β-lactam with β-lactamase inhibitors (BL-IBLs). These studies validate cefiderocol as a powerful option against *Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Burkholderia* spp, *S. maltophilia and Elizabethkingia meningoseptica* resistant to carbapenems [3,4].

Candel et al. [4] conducted a European multicenter study where they obtained 20,911 clinical samples collected between 2013-2018 in which they describe the activity of cefiderocol compared with ceftazidime-avibactam, ceftolozane-tazobactam and against colistin. The authors categorized the results according to site of infection, microorganism and against samples with different breakpoints of susceptibility to carbapenems.

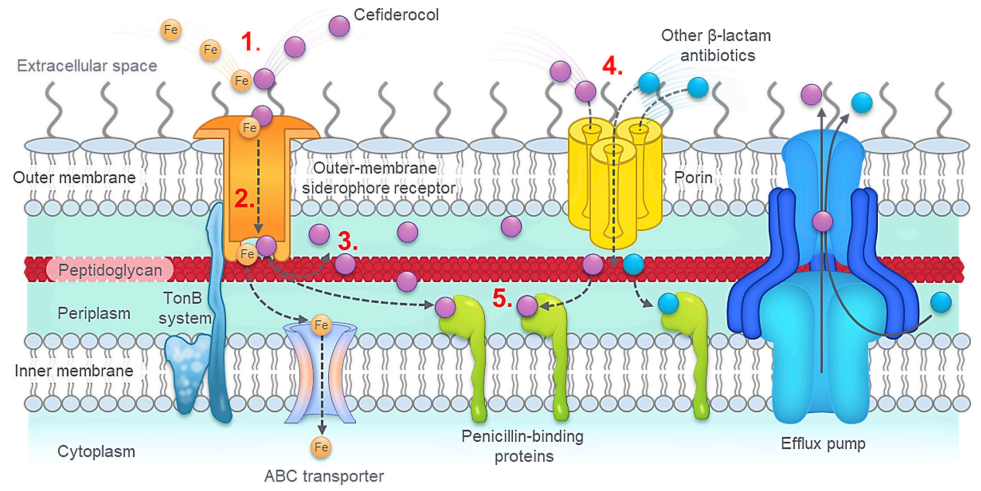

Figure 1 | **Mechanism of action of cefiderocol**

Cefiderocol showed excellent activity against all Gram-negative species (≥97%) regardless of key infection site and carbapenem MIC. In this study, 9,399 (34%) were respiratory samples from patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). In patients with this infection profile, cefiderocol maintained a high activity, sensitivity range of 93-100% for *Enterobacterales* samples, 92% for *Acinetobacter* spp, 99% for *P. aeruginosa*, 95% *Burkholderia* spp .and 100% of *S. maltophilia* strains [4].

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

In some subgroups of patients, with certain particularities, such as in critically ill patients, there is an increase in the volume of distribution, enhanced or reduced renal clearance, and hyperdynamic conditions, all factors that can produce inadequate plasma ß-lactams antibiotic concentration [5]. In these patients, these considerations are essential to optimize their antimicrobial therapy, taking into account pharmacokinetics and pharmacodynamics (PK/PD) [5].

Cefiderocol exhibits a mean elimination half-life of 2-3 h, with a protein binding of 58% and is excreted mainly by the renal route without changes [6]. Administration of higher doses of cefiderocol and prolonged infusion times according to PK/PD principles have been identified as strategies to optimize the effectiveness of ß-lactam antibiotics in this setting. The standard cefiderocol dose is 2000mg every 8h in extended perfusion over 3 h [6]. Cefiderocol shows physicochemical stability in syringes for 12 h, opening the possibility of continuous infusion [7]. The dose of cefiderocol requires dose adjustment based on renal function, either in dysfunction or in hyper-clearance states that require daily dose increase to 2000 mg every 6h with creatinine clearance >120ml/min [6].

In an intrapulmonary pharmacokinetic study in patients with severe pneumonia on mechanical ventilation treated with cefiderocol, it was observed how the antibiotic penetrates the epithelial lining fluid at concentrations similar to other cephalosporins and sufficient to inhibit Gram-negative microorganisms with MICs of ≤4 mg/L [8].

CLINICAL EXPERIENCE. FROM PIVOTALS TO CASE SERIES

Cefiderocol has been approved since 2019 by the FDA for the treatment of infections caused by susceptible Gram-negative microorganisms, encompassing complicated urinary tract infections (cUTI)and HABP/VABP, and by the EMA in 2020 for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The efficacy of cefiderocol has been assessed in three randomized clinical trials (RCTs). In a 2018 first phase-2 RCT(APEKs-cUTI) [9] achieved its non-inferiority target against imipenem with a primary endpoint of composite of clinical and microbiological outcomes at test of cure for the treatment cUTIs caused by Gram-negative. A total of 371 patients were enrolled on a modified intention-to-treat basis. The primary endpoint was attained by 73% (183/ 252) and 55% (65/119) of patients in the cefiderocol and imipenem-cilastatin arms respectively (adjusted difference: 18.6%; 95% confidence interval [CI]: 8.2 to 28.9). Microbiologic response was higher in patients treated with cefiderocol, with similar results in clinical response in both arms. Infections with carbapenem-resistant organisms were not admitted in this study. The most frequent uropathogens were E. *coli* and *K. pneumoniae*, while *P. aeruginosa* was isolated in less than 8%.

Subsequently, the EMA requested a new ECA to give its approval, which should include the infections with the greatest

need for this new antibiotic; carbapenem-resistant Gram-negative infections. With this objective, the CREDIBLE-CR [10] study was designed. CREDIBLE-CR trial was carried out to study the efficacy of cefiderocol for the treatment of life-threatening carbapenem-resistant Gram-negative infections (HABP; VABP; HCABP; cUTI, bloodstream infections or sepsis) with the best available therapy (BAT).

In this open-label multicentre RCT, 152 patients were enrolled in a 2:1 ratio to received cefiderocol (n= 101) or BAT (n= 49). The primary endpoint of this study was non-inferiority in terms of clinical cure and microbiological eradication in the test of cure. In the BAT arm, the combination of up to 3 antibiotics was allowed; in this arm the predominant antibiotic was colistin (66%). The addition of 1 antibiotic to cefiderocol, excluding colistin and BL-IBL, was allowed as well (20% of cases). The main endpoint of the study was achieved. However, when analyzing mortality, it was found that the group treated with cefiderocol had a higher mortality at days 14, 28 and end of study than those treated with BAT. This situation has led to a mortality warning from the FDA. Notwithstanding, it should be pointed out that this study had many limitations and design flaws that make it difficult to adequately interpret the excess mortality in cefiderocol arm. The first circumstance is that the study design was not programmed for a mortality endpoint. Hence, the small sample size and heterogeneous patient population limited the possible number of stratification factors for randomization, increasing the potential for imbalances in baseline factors that might have contributed to the difference in all-cause mortality. There is a great variability of treatments received and combinations. Heterogeneity was also observed in the microorganisms involved, with *Acinetobacter* ssp. being the most represented microorganism (n=54 [46%]), the second microorganism was *Klebsiella* spp (n=39 [33%]), followed in a low number of cases by *P. aeruginosa* (n= 22 [19%]), *S. maltophilia* (n=5 [6%]) and *E. coli* (n=1), therefore the interpretation of results according to microorganism is not possible. Moreover, this is a clinical trial carried out in critically ill patients, which by itself adds unavoidable confounding factors. Thereby, despite the higher mortality in this study, cefiderocol was approved by the EMA. for the treatment of infections due aerobic Gram-negative microorganism in adults with limited treatment options.

Last but not least, the APEKS-NP [11], is a multicentre double-blinded phase-3 RCT, in patients with HAP, VAP or health-care-associated Gram-negative pneumonia were randomly assigned in a proportion of 1:1 to receive cefiderocol or meropenem. All patients also received open-label intravenous linezolid for at least 5 days. Participants were stratified at randomization by infection type and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤ 15 and ≥16). The primary endpoint was all-cause mortality at day 14 in the modified intention-to-treat (ITT) population. A total of 292 patients were recruited (148 to cefiderocol and 152 to meropenem). Among these 199 (68%) were in the ICU, 60% were mechanically ventilated. The primary endpoint of all-cause mortality at day 14 in the modified ITT population was 12.4% for the cefiderocol group (18/145) and 11.6% for the meropenem group (17 /146); adjusted treatment difference 0.8%, 95% CI −6·6 to 8.2; p=0.002). All-cause mortality was also similar between groups at day 28. The microbiological data showed that 86% in both groups (124 in the cefiderocol group and 127 in the meropenem group) had a culture documented Gram-negative infection; *K. pneumoniae* n=92 (32%), *P. aeruginosa n*=48 (16%), *A. baumannii* n=47 (16%), and *Escherichia coli* n=41 (14%). In this study 18.6% (27/145) in cefiderocol arm and 13,6% (20/147) in meropenem arm were Gram-negative carbapenemase producers. For 16 patients with *Acinetobacter* spp and meropenem MICs higher than 64 mg/L, all-cause mortality at day 14 was 0% (0/5) in the cefiderocol group and 46% (5/11) in the meropenem group**.** The results of this study in pneumonia reinforce cefiderocol in the safety aspect, because there were no differences in both groups in adverse events and without problems in unexpected mortality resulting in the primary endpoint at 14-day mortality were similar in both arms. In this trial safety profile is consistent with other cephalosporins or carbapenems.

Numerous publications with clinical experience data with cefiderocol have added evidence and information on this antibiotic in real life, most reports have been in the population of patients treated for carbapenem-resistant *Acinetobacter*. Falcone et al [12] have described their experience in the treatment of MDR *A. baumannii* or other carbapenem-resistant Gram-negatives infections in 10 critically ill patients in which *A. baumannii* was isolated in 80%. The authors report clinical success and 30-day survival of 70% and 90%, respectively. Bavaro et al. [13] reported their experience with cefiderocol-based combination therapies as rescue treatment in immunocompromised, critically ill patients or in patients with post-surgical infections. Cefiderocol was used in 13 patients with previous therapeutic failure. 10/13 infections were caused by carbapenem-resistant *A. baumannii*, 1/13 by *KPC-K. pneumonia* and 2/13 by *P. aeruginosa* XDR. Microbiological eradication was achieved in 100%. The 30-day survival rate was 10/13. In an Italian multicentre observational study, Pascale et al. [14] analyzed the impact of cefiderocol use on outcome in patients admitted to the ICU for severe COVID-19 and further diagnosed with carbapenem-resistant *A. baumannii* infection. A total of 107 patients were included in the analysis. Among these, 42 were treated with cefiderocol as monotherapy, and the remaining patients were treated with colistin, mostly (82%) administered as combination therapy. Authors did not found differences between groups in 28-day mortality (57% mortality rate, cefiderocol 55% versus colistin 58% P= 0.70).

In 2021 IDSA Guidelines [15] cefiderocol was recommended as alternative treatment in carbapenem-resistant *Enterobacterales* infections outside of the urinary tract as pneumonia. In OXA-48 carbapenemase infections or unknown carbapenemase and as preferred treatment if metallo-ß-lactamase is identified. In the treatment of *DTR-P. aeruginosa* cefiderocol is one of the possibilities recommended as treatment of choice in pyelonephritis or cUTI and as alternative in other focus. In other guidelines, cefiderocol is considered the treatment of choice in critical patients with pneumonia caused by carbapenem-resistant *A. baumannii* [16]. The need to use cefiderocol in combination

in the treatment of severe Acinetobacter carbapenem-resistant infections is still debated.

CONCLUSION

Cefiderocol provides a solution to DTR-infections. There is no doubt that the activity of cefiderocol against metallo-β-lactamases is of special interest, since to date there is no other β-lactam with activity against these carbapenemases produced by *Enterobacterales* or non-fermenting microorganisms. Pending confirmation with clinical experience studies, the possibility of its use against other Gram-negative bacilli with few therapeutic options, such as *A. baumannii*, *Burkholderia cepacia*, and *S. maltophilia* [3,4] is encouraging. As a β-lactam, its performance in terms of PK/PD is predictable. Furthermore, although it has validated its efficacy in three RCTs, it needs more real-life experience to better approximate its effectiveness and safety profile on a case-by-case basis in the different MDR-microorganisms it covers in its broad spectrum.

CONFLICTS OF INTEREST

MCS has received honoraria for talks on behalf of Gilead Science, MSD, Pfizer and Shionogi. The other authors declare no conflicts of interest.

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New antimicrobial alternatives in the treatment of pneumonia

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Ceftolozane-tazobactam in nosocomial pneumonia

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ABSTRACT

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

Keywords: Ceftolozane-tazobactam, molecular structure, in vitro activity, pharmacokinetic-Pharmacodynamic profile, nosocomial pneumonia.

MOLECULAR STRUCTURE AND *IN VITRO* ACTIVITY

Ceftolozane-tazobactam (CT) is the fusion of two molecules. A modified cephalosporin and a beta-lactamase inhibitor. Ceftolozane has an aminothiadiazole ring in the side chain, which, like that of ceftazidime and other extended-spectrum cephalosporins, confers activity against Gram-negatives. Its oxime group confers stability against beta-lactamases and dimethylacetic acid gives it enhanced anti-pseudomonal activity. The difference between ceftolozane and ceftazidime lies in position 3 of the side chain: ceftolozane has a pyrazole (heavier) instead of the pyridinium (lighter) found in ceftazidime. The pyrazole ring confers a steric hindrance between the ceftolozane and the gateway to the binding pocket in the active site of beta-lactamase, thus preventing hydrolysis and ensuring stability against *ampC* (figure 1 and 2) [1,2]. The result of these structural changes is its potent inhibition of *PBP3* with high affinity for *PBP1b* and *PBP1c* of *Pseudomonas aeruginosa*, while maintaining stability against ampC-type beta-lactamases. In addition, it is less affected than other antipseudomonal drugs by changes in permeability, Gram-negative outer membrane efflux pumps, reduced uptake through porins or modification of PBPs. Ceftolozane has activity against Gram-negative bacilli carrying classical class A beta-lactamases (TEM-1 and SHV-1), but like ceftazidime or ceftriaxone, it is hydrolyzed by extended-spectrum beta-lactamases (ESBLs) or carbapenemases. The addition of tazobactam extends the activity of ceftolozane against ESBL-producing bacteria, especially *Escherichia coli* and some anaerobic species.

Data collected in the United States between 2011 and 2014 reported up to 97% susceptibility to CT in *P. aeruginosa*, including multidrug-resistant and carbapenemase-insusceptible strains [3]. Equivalent data were reported in the USA between 2015 and 2017, showing 97.5% susceptibility in *P. aeruginosa* ($MIC_{50/90}$, 0.5/2 mg/L), including multirresistant (82.8% susceptible to CT) and extensively resistant (82.9% susceptibility) isolates [4]. Sader *et al.* reported slightly reduced overall susceptibility rates in *P. aeruginosa* isolates from Europe, 86.3% (at 8 mg/L) and 84.5% (4 mg/L), respectively [5]. In two Spanish studies with more than 1400 *P. aeruginosa* isolates, CT activity exceeded 94% sensitivity, the most frequently expressed resistance mechanism was oprD + ampC (80%) and the clone, in more than 68%, was ST175 [6,7]. The antipseudomonal activity of CT remains stable (MIC ≤ 2 mg/L) even when the MIC of ceftazidime, cefepime or piperacillin-tazobactam rises above 32 and 128 mg/l in carbapenem-resistant strains [8].

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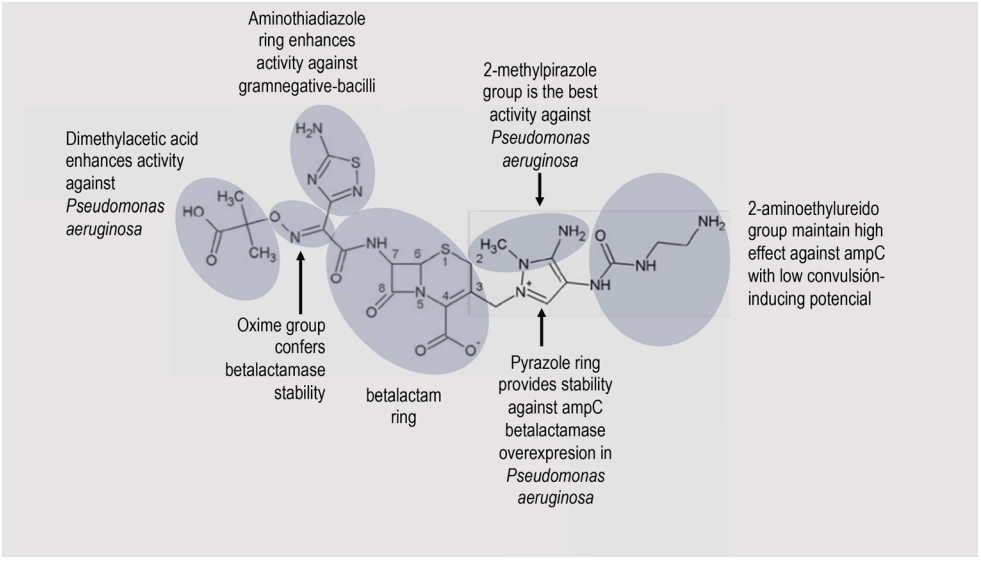

Figure 1 | **Structure–activity relationships for ceftolozane**

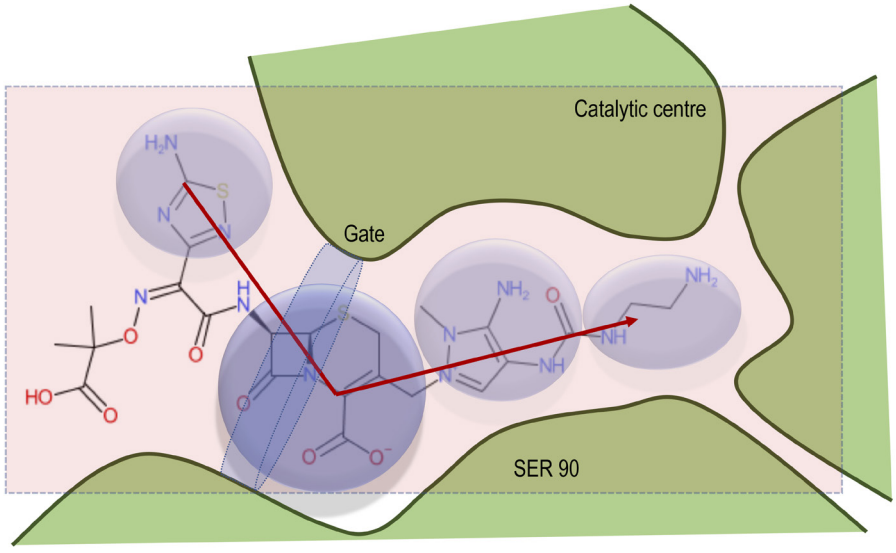

Figure 2 | **The gate of the 3-side chain binding pocket of AmpC b-lactamase and the chain of ceftolozane approaching (modified from reference 2)**

Analyzing activity against enterobacteria, Pazzini *et al* reported that CT was active against 85% of ESBL-producing *E. coli* isolates, in contrast to 57.5% of ESBL-producing *K. pneumoniae*. The CENIT study conducted on isolates from Spanish hospitals showed that CT was highly active not only against multidrug-resistant *P. aeruginosa*, but also against *E. coli*, including wild-type, *ampC* phenotype and ESBL-producing isolates. Activity decreased against the ESBL-producing strains *Klebsiella* spp. ($MIC_{50/90}$, 4/16 mg/L) and the combination was not active against carbapenemase-producing bacteria (MIC 64 mg/L) [9].

Results obtained from the follow-up study of respiratory samples conducted in American hospitals between 2013 and 2015 with more than 1,500 isolates of *P. aeruginosa* and more than 2,360 strains of *Enterobacteriaceae*, in which CT was shown to be the most active antibiotic against *P. aeruginosa*

and with activity against ESBL-producing *Enterobacteriaceae* isolates, detected in 13.4% of *E coli* and *K. pneumoniae* isolates. CT was active against $bla_{CTX\text{-}M\text{-}14}$-like and $bla_{CTX\text{-}M\text{-}15}$-like isolates. However, it was less active against $bla_{CTX\text{-}M}$ and had low activity against *Proteus* spp [10]. Taking clinical isolates from patients in the ASPECT-NP study, CT was active against more than 75% of *Enterobacteriaceae* isolates that did not carry carbapenemases and together with amikacin showed the highest activity against *P. aeruginosa* isolates [11].

Studies in patients with ventilator-associated pneumonia [12,13] caused by *P. aeruginosa,* showed high mortality rates if initial empirical antibiotic treatment is not appropriate. This has been replicated in other models of infection with high severity or greater inoculum effect such as bacteremia [14-16]. In these complex or severe infection models, the MIC and, if possible, the MPC (mutant preventive concentration) should be reached as soon as possible to prevent the antimicrobial from falling within the mutant selection window and to avoid intra- or post-treatment resistance. At MPC >32 mg/L for ceftazidime, cefepime, aztreonam, piperacillin-tazobactam and imipenem, the likelihood of serum concentrations of these antibiotics falling within the mutant selection window is very high, even when administered at maximal doses by prolonged or continuous infusion. The risk is moderate for meropenem (8 mg/L MPC) administered at doses of 6 g daily by prolonged infusion, and very low for CT (2 mg/L MPC) at doses of 3 g by 3-4-hour infusion every 8 h [17]. Also, cross-resistance between classical antipseudomonics may modify the emergence of resistance, so that CT could be a safe alternative in this type of infections.

Although CT has been shown to be the treatment of choice for *P. aeruginosa* infections, including multidrug-resistant and extensively resistant strains, some cases of resistance have also been reported. The most reported cause is associated with mutations in the *ampC* gene. The rate of development of this type of resistance ranged from 2-14% depending on the published series [18]. Another reason for resistance in treatment would be related to activity in the PDC-3 catalytic center of the *ampC* pocket [19]. These conformational changes in the PDC-3 loop are caused by the substitution of the amino acid E221K, which produces morphological and electrostatic modifications in the catalytic center. This facilitates the hydrolysis of ceftazidime, aztreonam, cefepime and ceftolozane. This mechanism has already been described in other species and for ceftolozane is estimated at 1.5% of isolates. Inhibitors (tazobactam, avibactam) partially restore this change. A final reason is the presence of other enzymes in the periplasmic space (OXA-17, OXA-24, MBL, GES).

PHARMACOKINETIC-PHARMACODYNAMIC PROFILE

Ceftolozane is an intravenous cephalosporin that exhibits linearity after single or multiple administrations. The mean Cmax after a 1 g dose of ceftolozane ranges from 58.4 mg/L to 92.3 mg/L and plasma half-life values range from 2.3 to 2.7 h. Protein binding of the drug is approximately 20%, and the volume of distribution is approximately 14 L [20]. It is eliminated by glomerular filtration; ceftolozane is minimally metabolized, and approximately 20% of tazobactam is metabolized by hydrolysis [21]. Ceftolozane is not a substrate of organic anion transporters organic anion transporters 1 and 3 (OAT1 and OAT3), whereas tazobactam is. Ceftolozane administration does not influence the clearance of tazobactam and increases the concentration of tazobactam [22].

CT is bactericidal, and the main pharmacodynamic parameter is time above MIC (for 40-50% of the dosing interval). In a population pharmacokinetic model to evaluate CT doses in nosocomial pneumonia through Monte Carlo simulations, a doubling of CT doses (2 g ceftolozane/1 g tazobactam) was found to substantially improve the number of patients achieving adequate time-above-MIC values. For MIC values up to 8 mg/L, the probability of target attachment (PTA) was 59-75% for doses of 1.5 g every 8 h, while for doses of 3 g every 8 hours, it was 88-96%. This manuscript justifies the dose of CT used in the clinical studies of patients with nosocomial pneumonia [23]. This dose of 3 g three times daily achieves sufficient PTA in populations with increased glomerular filtration rate ([CrCl] ≥ 130 mL/min)) [21], so common in the critically ill patient. Ceftolozane is also stable when reconstituted for more than 24 h at room temperature diluted in both saline and 5% dextrose, as demonstrated by particle degradation studies, in polyvinyl infusion systems or elastomeric pumps, as used in home hospitalization units [24].

Therefore, β-lactam antibiotics (except for imipenem) and especially CT should be administered at high doses, in prolonged or continuous infusion and after a loading dose. This recommendation is based on achieving several objectives: i) achieving time-dependent bactericidal activity, ii) the inoculum effect in foci with high bacterial load (present at the start of treatment), iii) ensuring the PK/PD ratio for high MIC against *P. aeruginosa*, iv) overcoming the changes that renal clearance may cause in drug distribution, and v) overcoming the preventive concentration of mutants in the infective focus [17]. This, as we shall see, is particularly indicated in nosocomial pneumonia.

CLINICAL EVIDENCE ON CEFTOLOZANE-TAZOBACTAM IN NOSOCOMIAL PNEUMONIA

In 2015-2016, after CT was approved at a dose of 1.5 g every 8 h in both complicated urinary tract infection and intra-abdominal infection, a pharmacokinetic model was used to justify dosing regimens in nosocomial pneumonia in phase 3 studies through Monte Carlo simulations. These showed that a 3 g dose of CT for nosocomial pneumonia patients with normal renal function is needed to achieve a PTA > 90% (98% actual) for the 1 log clearance target against pathogens with an MIC of ≤ 8 mg/L in ELF, compared to the approved 1.5 g dose for cIAIs and cUTIs [23].

With this approach, a randomized, controlled, dou-

ble-blind, non-inferiority trial was conducted in 263 hospitals in 34 countries to compare the activity of CT against meropenem in nosocomial pneumonia (ASPECT-NP study). Patients were randomly assigned to receive either 3 g of CT or 1 g of meropenem intravenously every 8 h for 8-14 days [25]. Seventy-one per cent of patients had ventilator-associated pneumonia, 33% had APACHE II scores equal or over 20, and 92% were in the intensive care unit. At 28 days, a quarter of patients in both groups had died (87 (24-0%) patients in the CT group and 92 (25-3%) in the meropenem group (weighted treatment difference 1-1% [95% CI -5-1 to 7-4]). At the test-of-cure visit 197 (54%) patients in the CT group and 194 (53%) in the meropenem group were clinically cured (weighted treatment difference 1-1% [95% CI -6-2 to 8-3]). Thus, CT was not inferior to meropenem in terms of either all-cause mortality at 28 days or clinical cure. In this study, 18% of patients enrolled in the CT group were bacteraemic vs. 11% in the meropenem group and 15% were from previous treatment failure vs. 11% in the meropenem group. These results led to U.S. Food and Drug Administration approval of CT for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in patients 18 years and older in June 2019 [26].

Clinical trials prior to ASPECT-NP on nosocomial pneumonia had generally shown a higher 28-day mortality in patients with ventilated hospital-acquired pneumonia than in those with ventilator-associated pneumonia [27]. In ASPECT-NP, a difference in mortality between the two conditions was observed only in the meropenem group. As a result, 28-day mortality in patients with ventilated hospital-acquired pneumonia was lower in the CT group than in the meropenem group. However, although the 95% CI for this treatment difference excluded zero, significance could not be inferred because analyses were not performed prospectively for both subgroups. In a *post-hoc* study, looking specifically at this group with ventilated HABP (vHABP), 99 participants in the CT arm and 108 in the meropenem arm, the odds of dying at day 28 from any cause were 2.3 times higher when participants treated with meropenem compared to those treated with CT [28].

The *post-hoc* study correlating prognosis in ASPECT-NP patients by each type of pathogen was performed. Pathogens isolated from lower respiratory tract samples were *K. pneumoniae* (34.6%), *P. aeruginosa* (25.0%) and *E. coli* (18.2%). Among the baseline *Enterobacteriaceae* isolates, 171/456 (37.5%) were ESBL positive. Susceptibility rates were 87.0% for CT and 93.3% for meropenem. 28-day all-cause mortality rates, clinical cure rate and microbiological eradication were comparable in both groups [29].

Johnson MG et al analyzed the emergence of resistance during treatment in *P. aeruginosa* isolates included in the ASPCT-NP study. Among the 59 isolates in the CT treatment arm, three (5.1%) had corresponding non-susceptible isolate pairs at baseline. Molecular analysis of these three isolates together with their reference pairs determined that two pairs had different sequence types and one pair had the same sequence type, thus only one could demonstrate the emergence of resistance during treatment. Among the 58 isolates in the meropenem treatment arm, 15 (25.9%) had corresponding pairs of non-susceptible isolates at the start of treatment. Molecular typing of these 15 isolates, together with their reference pair, determined that two pairs (3.4%) had different sequence types and that the other 13 pairs of isolates had the same sequence type. The most common molecular mechanisms of resistance found in the meropenem arm were *oprD* deficiency (n = 12 of 13; 92.3%) and overexpression of the protein and overexpression of the *MexXY* efflux system (n = 3 of 13; 23.1%) [30]. This study highlights the need to reach the MIC as soon as possible and if possible, the MPC to avoid falling into the resistance selection window. The risk is moderate for meropenem (MIC of 8 mg/L) administered at a dose of 6 g daily by prolonged infusion. However, the selection risk is very low for CT (2 mg/L MPC) at a dose of 3 g by 3–4-hour infusion every 8 h. We will observe over time whether the impact of the unavailability of CT during the COVID-19 pandemic might have generated more resistance in hospital-acquired ventilated *P. aeruginosa* pneumonia.

In conclusion, CT was clinically and microbiologically effective drug in the treatment of nosocomial pneumonia, stable at room temperature and safe at its approved dosage of 3g every 8 hours, which allows optimizing treatment in the frail or critically ill patient.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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Ceftazidime-avibactam

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ABSTRACT

The increase in nosocomial infections by beta-lactamase-producing Gram-negative bacilli constitutes a therapeutic challenge. The combination of ceftazidime-avibactam offers a very interesting therapeutic option for nosocomial pneumonia caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, multidrug-resistant *Pseudomonas aeruginosa*, and other enterobacteria. Compared to carbapenems, ceftazidime-avibactam has demonstrated non-inferiority in the treatment of nosocomial pneumonia including better clinical and microbiological cure rates and mortality compared to colistin. The limitation of ceftazidime-avibactam in the treatment of infections caused by metallo-beta-lactamase-producing *Enterobacteriaceae* can be overcome with the addition of aztreonam.

Keywords: Ceftazidime-avibactam. Nosocomial pneumonia. ESBL-producing *Enterobacteriaceae*.

INTRODUCTION

Despite the improvement in health care and the multiple recommendations on the prudent use of antibiotics, nosocomial pneumonia ranks second, after urinary infections of hospital-acquired infections, with an incidence of 5-20 cases for every 1000 admissions [1]. Ventilator-associated pneumonia is also not uncommon and can be found in 2-16 cases per 1000 days/ventilation. These infections lead to a greater use of antibiotics against microorganisms that will frequently present antibiotic resistance, so the challenge is choosing an antimicrobial capable of overcoming these resistances with the most adjusted spectrum. In this context, ceftazidime-avibactam (CAZ-AVI) is positioned as a useful tool for the treatment of these serious infections.

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MICROBIOLOGICAL PROFILE

CAZ-AVI is composed by a third-generation cephalosporin and a beta-lactamase inhibitor. Ceftazidime is a broad-spectrum third-generation cephalosporin. It has a bactericidal action by binding to penicillin-binding proteins (PBP) and then inhibiting the synthesis of the bacterial wall. It is active against a wide number of Gram-negative bacteria, including penicillinase-producing strains of *N. gonorrhoeae* and a large number of *Enterobacteriaceae* (*E. coli, Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., *Morganella* spp., *Proteus* spp., *Providencia* spp., *and Serratia* spp.) [2]. Ceftazidime is the cephalosporin with the highest activity against *Pseudomonas aeruginosa*.

Resistance to beta-lactams and cephalosporins is configured to a greater extent by the appearance of beta-lactamases. There are different types of beta-lactamases: class A, present in enterobacteria and in extended-spectrum beta-lactamase (ESBL) *Klebsiella* producer, class B, for which there are no inhibitors, class C, which is induced in Gram-negative rods, especially by the transmission of plasmids and those of class D where traditional beta-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam) do not have much effect [3].

Avibactam is a beta-lactamase inhibitor that does not have antibiotic activity "*per se*" and protects the action of ceftazidime. Its action profile is exerted mainly on class A and class C beta-lactams and to a lesser extent on class D. Avibactam has no effect on metallo-beta-lactamases (MBL) present in anaerobes and in some species of *Pseudomonas* spp. [4].

In the INFORM study, samples from lower respiratory track samples of patients with pneumonia hospitalized in 70 hospital centers were analyzed for one year (2017-2018), where the in-vitro activity of CAZ-AVI was studied [5]. The antibiotic susceptibility results for CAZ-AVI were 96% for *P. aeruginosa*, 100% for *E. coli*, and 100% for *Klebsiella pneumoniae*. When comparing the action of CAZ-AVI on carbapenemase-producing *Enterobacteriaceae* isolates, CAZ-AVI showed similar sen-

Table 1 Recommended dose for adults with estimated CrCl ≤ 50 mL/min.

Estimated CrCl (ml/min)	CAZ-AVI dose	Interval	Infusion time
31-50	1 g/0.25 g	q 8 h	2 hours
16-30		q 12 h	
6-15	0.75 g/0.1875 g	q 24 h	
Haemodialysis		q 48 h	

CrCl: estimated creatinine clearance using the Cockcroft-Gault formula

sitivity to colistin and tigecycline (73%, 77%, and 78.1%, respectively). Excluding those MBL-producing isolates, CAZ-AVI showed a sensitivity of 95.9% against carbapenemase-producing *Enterobacteriaceae* [6].

PHARMACOKINETIC-PHARMACODYNAMIC CHARACTERISTICS

The administration and dosage regimen is 2 g of ceftazidime and 0.5 g of avibactam in continuous infusion administered over 2 hours with a dosage of three times a day. CAZ-AVI exhibits linear pharmacokinetics. It is poorly bound to proteins and is not metabolized in the liver. Its excretion is renal, so the doses have to be adjusted in renal failure (Table 1). Like all beta-lactams, the predictive pharmacokinetic/pharmacodynamic (PK/PD) therapeutic efficacy index is the time during which free antimicrobial concentrations remain above the minimum inhibitory concentration (MIC) (%*f*T>MIC), expressed as percentage of the dosage interval [7]. The PK/PD parameter related to the efficacy of avibactam is the time during which blood concentrations are above the critical or threshold concentration (CT), which is the minimum concentration of avibactam below which no inhibition of beta-lactamases *in vivo* occurs (%*f*T > CT). The maximum concentration (Cmax) and area under the curve (AUC) increase proportionally with increasing dose of CAZ-AVI. The penetration of CAZ-AVI into the central nervous system is low.

For *Enterobacteriaceae*, suppression of regrowth within 12-24 h was obtained with ceftazidime 2 g every 8 h and continuous infusions of avibactam providing concentrations of 0.25-0.5 mg/L over 4.5 h so that a CT avibactam 0.5 mg/l is sufficient to achieve the pharmacodynamic target of CAZ/AVI against *Enterobacteriaceae*, while *f*T>CT values of up to 62.5% are required for *Pseudomonas*, with CT of 1 mg/ L, to achieve a bacteriostatic effect [8].

CLINICAL EXPERIENCE

The pivotal study for the comparison of CAZ-AVI versus meropenem in nosocomial pneumonia was the REPROVE study, which is a phase 3, multinational study involving 136 centers, double-blinded, and with a non-inferiority design [9]. Clinical cure, clinical response, and mortality outcomes of CAZ-AVI 2/0.5 g were compared. Similar clinical cure rates (67.2% vs. 69.1%; ITT difference -1.9; 95%CI -8.1,4.3) and mortality (9.6% vs. 8.3%; ITT difference 1.5; 95%CI -2.4,5.3) were observed in the comparison of CAZ-AVI with meropenem, thus demonstrating its non-inferiority in the treatment of nosocomial pneumonia.

Data from clinical experience in an outbreak of 57 patients with nosocomial infection by OXA-48-producing *Enterobacteriaceae* showed that CAZ-AVI used as salvage therapy showed clinical cure rates of 77%, microbiological cure of 65% and microbiological failure of the 10%. All isolates showed complete sensitivity to CAZ-AVI [9].

The use of CAZ-AVI versus colistin in the treatment of *K. pneumoniae* was analyzed in an observational, prospective, multicenter study where data were collected from 137 patients whose isolates came mainly from bacteremia (46%) and respiratory isolates (22%) in which 28% were treated with CAZ-AVI and 72% with colistin. Patients treated with CAZ-AVI had a 64% chance of a better outcome compared to those treated with colistin [10]. When CAZ-AVI has been used as salvage therapy, an improvement in the SOFA score has been observed in patients with bacteremia due to carbapenemase-producing *K. pneumoniae* [11].

One of the potential limitations in the use of CAZ-AVI is infections by metallo-beta-lactamase-producing Enterobacteriaceae, where this antibiotic will not be effective. The combination of aztreonam with CAZ-AVI makes it possible to overcome resistance due to the production of MBLs by enterobacteria. This combination allows simultaneous inhibition of multiple PBPs. Data from in-vitro and observational studies have shown that the addition of aztreonam to CAZ-AVI for bacteremic infections with MBL-producing *Enterobacteriaceae* leads to improved outcomes. The 30-day mortality of the combination versus treatment with other antibiotics was significantly lower for the CAZ-AVI and aztreonam group compared with other antibiotics (hazard ratio [HR], 0.37 [95% confidence interval: 0.13-0.74]; p =0.01) and also clinical failure at 14 days and hospital stay [12,13].

Therefore, CAZ-AVI offers very good antibiotic coverage for patients with pneumonia caused by beta-lactamase-producing Gram-negative bacilli. The limitation of CAZ-AVI for the treatment of MBL-producing *Enterobacteriaceae* can be overcome with the addition of aztreonam.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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New evidence in severe pneumonia: meropenem-vaborbactam

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ABSTRACT

The appearance and spread of new mechanisms of bacterial resistance to antibiotics is a serious health problem. One of the most difficult resistance mechanisms to treat is the production of carbapenemases. Carbapenemase KPC is one of those mechanisms with few therapeutic options. Meropenem-vaborbactam has shown great efficacy against this type of microorganism, both from a clinical and microbiological point of view. Its good pharmacokinetics, including in the lung, and its safety profile make meropenem-vaborbactam an excellent therapeutic option. Finally, the absence of resistance genesis during treatment seems to indicate that its efficacy will be long-lasting.

Keywords: Gram-negative bacteria, multiresistant *Enterobacteriaceae*, ceftazidime-avibactam, meropenem-vaborbactam,

INTRODUCTION

The combination of carbapenem (meropenem) with the beta-lactamase inhibitor vaborbactam is one of the latest therapeutic novelties available on the market. Meropenem-vaborbactam (MV) represents an important therapeutic advance due to its wide antimicrobial spectrum that includes the dreaded carbapenemase KPC, its clinical efficacy, its correct pharmacokinetic profile and its large safety margin.

MICROBIOLOGY

In addition to the usual coverage of beta-lactams, MV is effective against type A and C beta-lactamases. Among them, the KPC type carbapenemase (class A) is one of the most frequent and difficult to treat threats among the resistances developed by Gram-negative bacteria. This type of resistance is widely distributed in the United States and multiple papers from that area demonstrate the ability of MV to treat KPC producing *Enterobacteriaceae* [1,2].

Clinical experience with MV has shown the absence of resistance development with exposure to the drug. Lomonovskaya assessed patients treated with MV in Tango II clinical trial and found only 1 of 50 patients treated an increase in MIC from 0.25/8 to 1/8 mg/L (within the susceptibility range). This aspect is of great interest in contrast to the findings detected with the treatment of KPC enterobacteria with ceftazidime-avibactam. In vitro exposure to this drug causes a mutation in the "omega loop" of the KPC enzyme that manages to increase its hydrolysis capacity on ceftazidime and overcomes the effect of avibactam. In parallel, a recovery of susceptibility to meropenem is observed, but not in a lasting way. This resistance phenomenon has been observed in the clinical practice [3-8] (Table 1).

Table 1 **Development of resistance to ceftazidime-avibactam.**

Study (year)	Development of resistance to ceftazidime-avibactam
Shields et al, 2016 [3]	8.1% (3/37) after 10-19 days of treatment
Lomonovskaya et al, 2017 (from Tango II study) [4]	25% (1/4)
Giddins et al, 2018 [5]	1 clinic case
Gaibani et al, 2018 [6]	
Athans et al, 2019 [7]	1 clinic case
Tumbarello et al, 2022 [8]	59,5% of strains resistant to ceftazidime-avibactam

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Vaborbactam, for the time being in union with meropenem, administered together with aztreonam has been shown to be effective in the *in vitro* treatment of metallo-beta-lactamases that coincide with a beta-lactamase that otherwise would inhibit the efficacy of aztreonam [9].

PHARMACOKINETICS/PHARMACODYNAMICS

Preclinical and clinical data have shown good pharmacokinetic parallelism between the two components of MV, and a predictable PK that maintains correct plasma concentrations with the dose of 4 g (2g/2g) of MV administered every 8h in a 3 hour infusion for all strains with a MIC equal to or lower than 8 mg/l (10). Intravenous dose adjustment is recommended in patients with renal insufficiency (eGFR < 50 ml/min/1,73 m^2 or ACr ≤ 39 ml/min). In case of critically ill patients treated with continuous hemodialysis the MV dose will be 2 g (1 meropenem + 1 vaborbactam) in 3 h infusion every 8h [11].

One of the most frequent infectious focus in the critically ill patient, and one that also poses a pharmacokinetic challenge, is the lung. MV was evaluated in 10 healthy subjects with plasma and alveolar epithelial fluid sampling and a plasma/alveolar fluid ratio of 65% and 79% was obtained for the two components of MV, respectively [12]. Therefore MV is a correct choice for the treatment of pneumonia from the Pk point of view.

CLINICAL EXPERIENCE

Tango I and Tango II clinical trials provided MV indication for: complicated urinary tract infection (including pyelonephritis), complicated intraabdominal infection, in-hospital pneumonia (including ventilator-associated pneumonia), bacteremia occurring in conjunction with, or suspected to be associated with, any of the above infections, and the treatment of infections due to aerobic gram-negative microorganisms in adults with limited treatment options [4,13].

The results of the Tango II trial are of particular interest for the critically ill patient. Both clinical and microbiological responses were better in the MV-treated group compared to patients treated with best available therapy. Although not statistically significant, survival was also superior in the MV group. Since the control group included the use of aminoglycosides and/or colistin, renal adverse effects were more frequent in this group [4]. Basetti *et al* performed a post hoc analysis of the subgroup of patients treated with MV or best available therapy in the first line of treatment; this analysis showed a potentiation of the positive results of MV [14].

Three recent publications have shown clinical outcomes with MV used in care. In 2020 Shields *et al* published a prospective series including 20 patients, most of them (70%) were admitted to ICU and most of the strains (90%) were *Enterobacteriaceae* with KPC. MV was administered as monotherapy in 80% of the cases. Clinical and microbiological response was obtained in 65% of cases. Mortality in the series was strikingly low; 10% at day 30 and 20% at day 90 of evolution. Only one case of serious adverse event was described: eosinophilia that responded to treatment cessation [15].

In 2020 Alosaimy *et al* published a retrospective registry that included 40 patients (70% of them in ICU). Most strains were carbapenem-resistant enterobacteria (86,7%). MV was administered as monotherapy in 62% of cases and as rescue treatment in 27,5%. A correct clinical response was achieved in 70% of patients. It is of interest that the lack of response could be related to a late onset of MV (>72 h). One case of Steven-Johson syndrome was described as an adverse effect [16].

Finally in 2022 Tumbarello *et al* published the results of a retrospective registry on the compassionate use of MV in 12 Italian hospitals. 37 cases were collected; 23 bacteremias, 10 respiratory infections, 2 urinary tract infections, 1 soft tissue infection, 1 abdominal infection. Again 70% of the patients were admitted to the ICU. MV was used in monotherapy in 14 patients (38%) and the median time between clinical onset and treatment was 5 days. An interesting fact is the frequent presence of resistance to ceftazidime-avibactam observed, even without previous exposure to the drug (59,5%). Clinical cure was obtained in 28 of the treated cases (75,6%). Three patients suffered a recurrence of infection that was successfully treated with a second course of MV treatment. Nine patients died (24,3%); six of these patients started treatment with MV with a lag time of more than 48h from the onset of the clinic. There were no cases of development of resistance to MV during treatment [8].

CONCLUSIONS

MV is a highly effective option for the treatment of all types of infectious focus, especially when the etiological agent is a KPC-producing. Its pharmacokinetic and safety profile make the drug an excellent option for the critically ill patient. Compared to ceftazidime-avibactam MV does not induce the development of intra-treatment resistance.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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New antimicrobial alternatives in the treatment of pneumonia

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New evidence in severe pneumonia: imipenem/cilastatin/relebactam

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ABSTRACT

Imipenem combined with beta-lactamase inhibitor relebactam (IMI/REL) has an extensive bactericidal activity against Gram-negative pathogens producing class A or class C beta-lactamases, not active against class B and class D. The phase 3 clinical trial (RESTORE-IMI-2), double-blind, randomized, evaluated IMI/REL vs. piperacillin-tazobactam (PIP/TAZ) for treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), demonstrated non-inferiority at all-cause mortality at 28 days (15.9% vs 21.3%), favorable clinical response at 7-14 days end of treatment (61% vs 59.8%) and with minor serious adverse effects (26.7% vs 32%). IMI/REL is a therapeutic option in HAP and VAP at approved dosage imipenem 500 mg, cilastatin 500 mg and relebactam 250 mg once every 6h, by an IV infusion over 30 min.

Key words: Carbapenem resistant; Hospital acquired pneumonia; ventilator-associated bacterial pneumonia, nosocomial pneumonia.

INTRODUCTION

Early selection of the appropriate antibiotic in severe infections significantly reduces mortality. The increased use of carbapenems has led to the development of bacterial strains producing carbapenemases. *Enterobacterales* harboring class A carbapenemase (KPC, *Klebsiella pneumoniae* carbapenemase) constitute a problem within hospital infections. IMI/REL is a new antibiotic combination, bactericidal by its binding inhibition to penicillin binding proteins (PBP1 and PBP2). Recently, it has been approved by the FDA for use in ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) in June 2020 [1-3].

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MICROBIOLOGICAL PROFILE

The importance of beta-lactamase inhibitors goes back to early 1970s, when clavulanic acid was discovered, and soon after, sulbactam and tazobactam were added to the therapeutic arsenal. beta-lactamase inhibitors can restore the activity of the beta-lactam antibiotics by inhibiting bacteria beta-lactamases. Recently, at least 2 new groups of inhibitors have appeared: diazobicyclooctanes (DBOs) (as avibactam and relebactam) and boronic acid derivatives (as vaborbactam) [4]. Relebactam is a non-beta-lactam compound formed of a five-membered diazabicyclooctane ring with an amide group. It targets the active-site of serine beta-lactamases via carbamylation. Moreover, the piperidine ring at the 2-position carbonyl group provides a positive charge that prevents its efflux from bacterial cells [4].

Relebactam has no intrinsic antibacterial activity by itself and usually inhibits acquired and intrinsic beta-lactamases. It protects imipenem from degradation by Ambler class A (such as KPCs) and class C (such as AmpC) beta-lactamases and *Pseudomonas*-derived cephalosporinases. However, relebactam is not active against class B metallo-beta-lactamases or class D oxacillinases. In vitro, relebactam addition decrease the minimum inhibitory concentration (MIC) of imipenem by 2- to 128-fold against extended spectrum beta-lactamase (ESBL) or KPC-producing *Enterobacterales* [1].

From February to May 2013 a multicentre study was performed in 34 Spanish hospitals collecting 245 carbapenemase positive clinical isolates. *K. pneumoniae* was the specie most frequently isolated (74%) and carbapenemases belong to the following groups: OXA-48 (74%), metallo-beta-lactamase (24%) and KPC (2%) [5]. Data obtained in Hospital Universitario de La Princesa during 2020-2021 showed similar results (Table 1).

IMI/REL susceptibility rates were >90% against seven of the ten most found Enterobacterales species collected world-

Table 1 **Type of carbapenemase detected in carbapenemase producer *Enterobacterales* isolated during 2020 and 2021 in Hospital Universitario de la Princesa.**

	E. coli	*E. cloacae*	*K. pneumoniae*
KPC		2 (1.8%)	18 (4.4%)
OXA-48	22 (81.5%)	71 (65.8%)	358 (88.4%)
VIM	5 (18.5%)	35 (32.4%)	29 (7.2%)
Total number included	27	108	405

wide as part of the SMART 2017 surveillance program [1]. The susceptibility rates were *Escherichia coli* 99.6%, *K. pneumoniae* 93.0%, *Enterobacter cloacae* 96.8%, *K. oxytoca* 99.4%, *K. aerogenes* 97.6%, *Citrobacter freundii* 98.9% and *C. koseri* 99.8%. IMI/REL demonstrated modest or weak activity against *Serratia marcescens* 70.6%, *Morganella morganii* 32.0% and *Proteus mirabilis* 63.0%. Imipenem shows decreased activity against *Morganella*, *Proteus* and *Providencia* species due to a mechanism independent of beta-lactamase production so, it is not restored by a beta-lactam inhibitor [1]. IMI/REL also demonstrated potent *in vitro* activity against *P. aeruginosa* isolates [6]. Castanheira et al. tested IMI/REL in 45 carbapenemase-negative carbapenem-resistant *Enterobacterales* collected in US hospitals during 3 years with different resistance mechanisms as porin alterations, hyperproduction of efflux system or elevated expression of intrinsic and acquired beta-lactamases and IMI/REL inhibited 88.9% of the strains tested and 93% when *Proteus mirabilis* were not included [7].

To sum up, IMI/REL is active against a wide variety of Gram-negative pathogens, including KPC- and ESBL-producing isolates from different species of *Enterobacterales* and extensively drug-resistant *P. aeruginosa*, both imipenem-resistant strains due to OprD deficiency and GES-1, PER-1 and extended-spectrum OXA enzymes producers [4].

PHARMACOLOGICAL PROFILE: PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetics of imipenem/cilastatin are not affected when coadministered with relebactam. The Cmax and AUC of IMI/REL increase in proportion to dose. The elimination half-lives (t1/2) of IMI/REL are independent of dose. The binding of imipenem and cilastatin to human plasma proteins is approximately 20% and 40% respectively. The binding of relebactam to human plasma proteins is approximately 22% and is independent of concentration. When imipenem and cilastatin are given concomitantly, adequate levels of imipenem (approximately 70% of the dose) are achieved in the urine enable antibacterial activity. Cilastatin and relebactam are mainly eliminates in the urine as unchanged parent drugs. IMI/REL is mainly excreted by the kidneys, involving both glomerular filtration and active tubular secretion. The mean terminal elimination half-lives of imipenem/cilastatin and relebactam are 1.0 h and 1,2 h, respectively. Sex, race, age and weight have no clinically relevant effects on de pharmacokinetics of IMI/REL. The safety and efficacy of IMI/REL in children and adolescents below 18 years of age have not yet been established, no data are available. Hepatic impairment is not likely to have any effect on IMI/REL exposures, as the drugs are primarily cleared renally. No dose adjustment is required in patients with impaired hepatic function. Drug-drug interactions when co-administered with CYP inhibitors or inducers are unlikely. Based on reports of the concomitant use of imipenem/cilastatin, coadministration of IMI/REL with the anticonvulsant valproic acid/divalprox sodium or the antiviral ganciclovir is not recommended. Patients who have a CrCl less than 90 mL/min require dosage reduction. Patients with CrCl less 15 mL/min should not receive IMI/REL unless haemodialysis is instituted within 48 hours. There is inadequate information to recommend the use to patients undergoing peritoneal dialysis [1,8].

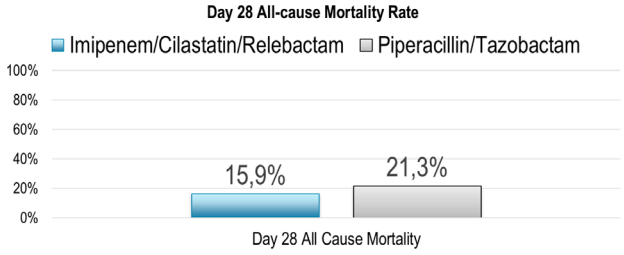
CLINICAL EVIDENCE

Preclinical studies, phase 1, dose-ranging and pharmacokinetic analysis support imipenem 500 mg/cilastatin 500 mg with 250 mg relebactam every 6 h. This dose showed efficacies in the RESTORE IMI-1 study, a multicenter, randomized, double blind trial comparing efficacy and safety the IMI/REL vs colistin and imipenem in patients with imipenem non susceptible bacterial infections, showing that IMI/REL was effective and well-tolerated in this patient profile [9].

The study RESTORE IMI-2 was phase 3, randomized, double-blind, no inferiority trial evaluating IMI/REL vs PIP/TAZ for HAP/VAP. Inclusion criteria were patients ≥18 years old requiring intravenous antibiotics for non-ventilated HAP, ventilated HAP or VAP. A lower respiratory tract sample was collected 48h before randomization. Exclusion criteria: the previous taking of antibiotics, isolation of only Gram-positive microorganisms in respiratory sample, creatinine clearance <15mL/min or need for dialysis, suspicion of non-bacterial pneumonia, obstructive pneumonia due to suspicion of cancer, immunodeficiencies, drug interaction and survival <72h and diseases such as tuberculosis, cystic fibrosis, or endocarditis.

Patients were randomized 1 IMI/REL:1 PIP/TAZ and stratified by ventilated or unventilated HAP/VAP and by Acute Physiology and Chronic Health evaluation II (APACHE II) score <15 vs ≥15. The treatment was 7-14 days, 14 days if pneumonia was associated with detection of *P. aeruginosa* or bacteremia. All patients received empirically linezolid (600 mg/12h) intravenous, until the existence of methicillin-resistant *S. aureus* (MRSA) was ruled out. If MRSA was present, linezolid was continued ≥7 days or ≥14 days if there was MRSA bacteremia. The visits were developed on day 1 (randomization), 3, 6, 10, EOT (end of therapy), EFU (early flow up) and 28 days. Respiratory samples were collected on EOT and EFU days. Clinical symptoms and signs and adverse effects were monitored daily. Chest X-ray was performed before randomization, EOT, EFU

A.



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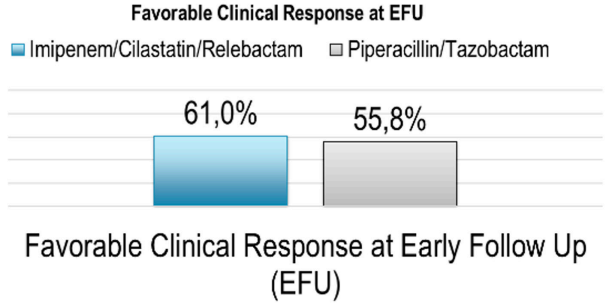

Figure 1 | **RESTORE IMI-2 Study: A) Day 28 all-cause mortality rate. B) Favorable Clinical Response at early follow up (EFU).**

and at 28 days. The identification and susceptibility of pathogens were confirmed in the central reference laboratory. Intermediate-susceptible pathogens were classified as non-susceptible.

The primary endpoint of the study was mortality at 28 days from any cause, the secondary endpoint of favorable clinical response in EFU (favorable with clinical resolution or unfavorable). Other secondary objectives were mortality at 28 days in the different subgroups, microbiological response (eradication or persistence of pathogens) in EOT and EFU. Mean treatment duration was 8,7 IMI/REL and 8,3 days with PIP/TAZ. The study was carried out in 113 hospitals of 27 countries from January 2016 to April 2019, 535 patients were randomized (266 IMI/REL, 269 PIP/TAZ). 66.1% were in intensive care units, 48.6% had ventilated HAP/VAP, 42.9% were >65 years, and 24.7% had moderate/severe renal impairment. The most frequent bacteria isolated were *K. pneumoniae* (25.6%), *P. aeruginosa* (18.9%), *Acinetobacter calcoaceticus-baumannii* complex (15.7%) and *E. coli* (15.5%) [10].

IMI/REL was noninferior to PIP/TAZ (Figure 1A and 1B) for the primary endpoint of mortality at day 28 (15.9% vs 21.3%; adjusted a treatment difference -5.3% [95% CI -11.9% to 1.2%]; no inferiority p<0.001). In the subgroups of ventilated HAP/VAP as well as in the subgroup of patients with APACHE II score ≥ 15, mortality was lower with IMI/REL than PIP/TAZ. IMI/REL was also noninferior for the key secondary endpoint of favorable clinical response (61% vs 55.8%) p<0,001 (adjusted treatment difference, 5% (95% CI -3.2% to 13.2%). In the different subgroups of patients, they were comparable, except in those with APACHE II score ≥ 15, where the clinical response was higher in IMI/REL. In the other secondary endpoints, overall microbiologic response at EFU, outcome was comparable between treatments. Most patients (85% vs 86.6%) had more than 1 adverse effect, more frequent in IMI/REL were diarrhea and increased transaminases. 6 patients with IMI/REL and 4 with PIP/TAZ discontinued treatment [10].

CONCLUSION

Relebactam is a class A and class C beta-lactam inhibitor. IMI/REL was effective in KPCs and *P. aeruginosa* resistant to carbapenems (non-metallo-carbapenemase) and showed no PIP/TAZ inferiority in HAP and VAP (RESTORE IMI-2 study). IMI/REL is indicated in HAP and VAP in adults, as well as infections due to Gram-negative aerobic organisms in adults with limited treatment options.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Update in SARS-CoV-2 pneumonia

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Ventilation support in SARS-CoV-2 pneumonia. Strategy and indications

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ABSTRACT

The SARS-CoV2 pandemic has generated a need for knowledge, new concepts in pathophysiology and an increase of the use of respiratory support in highly complex patients. This fact has provoked the need to evolve to the concept of personalized ventilatory support according to the patient's response to treatment.

Keywords: personalized mechanical ventilation, COVID-19, ARDS, protective ventilation.

INTRODUCTION

Ventilatory support in SARS-CoV2 pneumonia is not very different from ventilatory support in acute respiratory distress syndrome (ARDS) with different etiology. Although multiple controversies have been generated, what is clear is the need to evolve towards adequate high-level ventilatory support where we can manage patients in a personalized manner, applicable both to COVID-19 pneumonia and to any etiology of ARDS.

As in other pathologies, in ARDS the same treatment should not be indicated in all disease spectra, nor in different patients due to individual variability, nor in each patient throughout the time of disease progression. The concept of phenotypes and even chronotypes has been highlighted and the appropriate therapy should be assessed in each case. It is equally important to minimize management differences between prescribers and adopt homogeneous objectives and criteria by creating respiratory management protocols that ensure a common strategy.

The important idea to conveyed in this article is the evolution of mechanical ventilation towards high-level personalized respiratory support. This will consist of individualizing the application of ventilatory modes, parameters (not only PEEP), non-ventilatory therapies and oxygenation systems, evaluating changes in response without forgetting the critical patient on mechanical ventilation is a dynamic patient.

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DEFINITION OF ARDS

Berlin's definition (2011) to categorize ARDS based on the degree of hypoxemia [1], showed by the PaO2/FiO2 ratio, has been widely used to guide the management of SARS-CoV-2 patients. However, this definition has been shown to be limited for the adequacy of respiratory therapies. This idea had been previously expressed by different authors who advocate redefining distress and establishing the ventilatory strategy, not only considering oxygenation but also stratifying severity by considering lung compliance and alveolar dead space [2]. In this way we can establish different treatment strategies, using the appropriate PEEP in each patient, the appropriate tidal volume, as well as noninvasive ventilatory support strategies and extracorporeal techniques.

PATHOGENESIS OF ARDS IN COVID-19

ARDS caused by SARS-CoV-2 behaves like a traditional acute respiratory distress syndrome (hyaline membranes, progression through pathologic stages...) with a key role in intravascular immuno-thrombosis [3] and alteration of the hypoxic pulmonary vasoconstriction reflex [4]. This means that hypoxemia is not only related to pulmonary mechanics and decreased compliance but also due to the imbalance in the ventilation/perfusion ratio (V/Q) that leads to situations of very severe hypoxemia difficult to manage.

A study shows how virus involvement in extrapulmonary areas can also affect gas exchange. COVID 19 infiltration of carotid body receptors [5] that stimulate the respiratory center in

response to hypoxemia was evidenced. This could explain both the abnormal response to hypoxemia ("happy hypoxemia") and the increase in inspiratory drive.

Inspiratory drive increases transpulmonary pressure and could explain the phenomena of pulmonary rupture and mediastinal emphysema evidenced in these patients, generating lung damage and complicating the mechanical ventilation management.

PHENOTYPES

Stratification of patients into different phenotypes is necessary. Two phenotypes were initially established [6]: Type L (low) and Type H (high) referring to two forms of presentation of ARDS. Type L where the imbalance in V/Q ratio predominates, with a significant increase in alveolar dead space as a cause of hypoxemia. And Phenotype H characterized by alteration of respiratory mechanics with loss of pulmonary compliance and increased CT involvement. Each phenotype would require a different ventilatory strategy.

However, it could not be two different forms of presentation but different stages that may be produced by different reasons, for example, start or not of noninvasive support. According to a recently published article [7], phenotype is not the only important thing but also the pattern the patient will develop throughout the evolution of the disease.

MORTALITY IN MECHANICAL VENTILATION

The mortality of patients on mechanical ventilation has been high. Some studies [8] estimate an overall mortality of 52%, reflecting a large variability between different hospitals that cannot be explained by factors inherent to the patients themselves. It is postulated that factors such as the structural organization of the intensive care units, the availability of qualified personnel (nursing and physiotherapy care), the prevention of associated infections, as well as the adequate and early respiratory support with an early strategy of prone ventilation may have an influence.

HIGH-LEVEL PERSONALIZED VENTILATORY SUPPORT

We recommend a treatment using a strategy of pulmonary and diaphragmatic protection, individualizing and selecting the ventilatory parameters according to the mechanical characteristics of the lung. Adequate sedation strategy that allows optimal synchrony patient-ventilator, proper selection of PEEP and tidal volume offering protective ventilation. In this way we manage to avoid lung damage which could affect the prognosis of the patients.

There is a pyramid of respiratory support. In critically ill patients, invasive mechanical ventilation is essential. Moreover, there is a whole spectrum of respiratory support treatments with oxygenation systems (conventional and high flow), non-invasive mechanical ventilation and support with extracorporeal techniques such as extracorporeal membrane oxygenation (ECMO) and extracorporeal CO_2 extraction ($ECCO_2R$).

Based on evidence, we recommend developing a protocol where the first step is to provide noninvasive ventilatory support. We recommend using a combined strategy, high-flow nasal cannula (HFNC) associated with continuous positive airway pressure (CPAP), to reduce the problems of each technique and reduce the failure rate. Perkins et al [9] demonstrated the superiority of CPAP over HFNC to improve oxygenation. Many patients benefit from the use of both techniques with suitable monitoring using the ROX index [10] and the HACOR score as predictors of therapy failure. But the most important aspect is the monitoring of tachypnea and increased work of breathing in patients.

Early identification the patients who require endotracheal intubation and invasive mechanical ventilation is really fundamental. The classic criteria for intubation include hypoxemia with cardiovascular dysfunction, low level of consciousness and, perhaps the most important, inability to maintain the necessary work of breathing. The indication for intubation should be individualized, without forgetting the pulmonary collapse due to disease progression.

During invasive mechanical ventilation, it is essential to use a protective ventilation strategy that minimizes lung stress, strain and strain rate, looking for the minimum driving pressure with a homogeneous ventilation [11]. In this respect it is recommended to use a five-pillar protocol: first make a pulmonary mechanics diagnosis; PEEP titration to choose the most appropriate level based on the best global compliance, and in selected cases use Electrical Impedance Tomography (EIT) to monitor regional changes (Figure 1); then adjust ventilation to the minimum tidal volume and driving pressure. Work of breathing should be measured and alveolar dead space monitored using capnography; and finally assess the possibility of respiratory drive by closely monitoring of airway occlusion pressure (P0.1) [12].

A PEEP level should be selected according to the patient's need at each specific phase of the treatment. Based on the evidence, the level of PEEP will vary over time, depending on the phase of the disease and the treatment strategies employed.

All of that should be adjusted according to the patient's characteristics. In patients with morbid obesity or elevated intra-abdominal pressure these protective limits can be exceeded.

The protocol should consider early application of prone position to improve the oxygenation and also in situations of low pulmonary compliance. Prone is considered the treatment of choice for severe refractory hypoxemia [13] in patients with a PaO2/FIO2 ratio less than 150 mm Hg or decreased lung compliance, clearly improving patient mortality. Prone position is the great lung recruitment maneuver.

Prone awake has also been discussed as another option in the management of these patients, although there is still

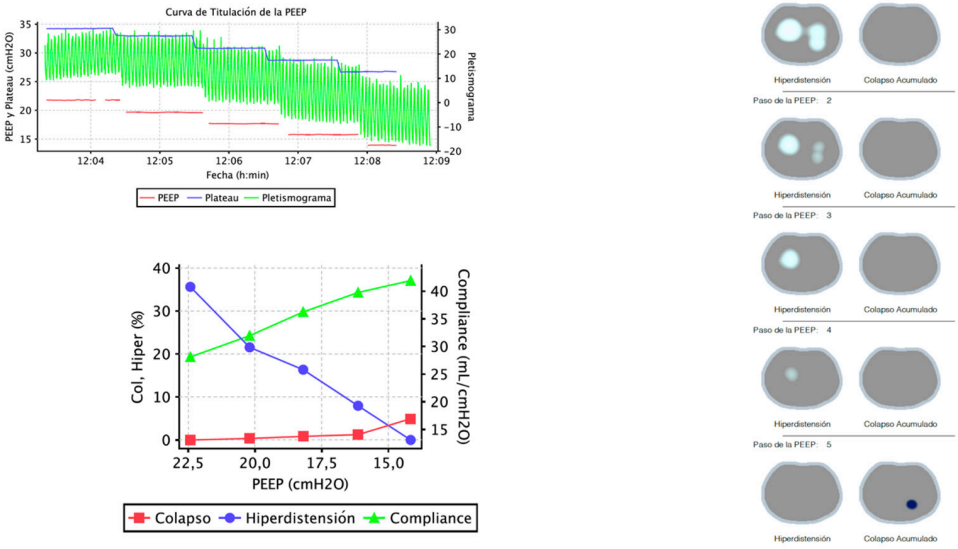

Figure 1 | **Pulmonary mechanics with PEEP titration by impedance tomography looking for the balance between pulmonary recruitment and overdistension.**

no high-quality evidence available to make a generalized recommendation. Ehrmann et al. [14] suggest it can improve oxygenation with a very low complication rate in selected patients with close monitoring. There are no clinical trials demonstrating that prone awake can truly decrease intubation rates and improve patient outcome and mortality.

If despite protective mechanical ventilation strategy and prone maneuvers we do not obtain the desired results, we have the option of ECMO. We must consider that patients who require ECMO are patients with high mortality because they did not respond to prone position. A Spanish case series study has been published [15] based on an observational cohort study that confirms a high mortality of patients receiving ECMO, up to 60%.

A promising technique in refractory cases is extracorporeal CO_2 extraction ($ECCO_2R$) [16]. It is a feasible technique using low blood flows that may represent a new therapeutic option combined with a protective and personalized ventilation strategy.

Another important aspect in the management of this type of patient is the work carried out by physiotherapists in ICU through respiratory rehabilitation and early mobilization, treatment by nursing staff in the prevention of infection, psychological support for patients, as well as treatment plans at discharge from ICU.

CONCLUSIONS

ARDS caused by COVID-19 pneumonia behaves similarly to distress of other etiology. Nevertheless, it presents particularities that require an individualized treatment strategy following a well-defined protocol. Mechanical ventilation conditions prognosis and mortality in these patients. It is recommended that the ventilatory strategy be dynamic during evolution and individualized to the requirements of each patient. It is essential to pay attention to the pillars of protective ventilation (tidal volume, lung distension pressure, respiratory drive...) avoiding pulmonary overdistension as a cause of avoidable damage. The treatment of lung collapse is basic, find the optimal PEEP at each moment and valuing the early prone as the main recruitment maneuver. To achieve this, measurements of pulmonary mechanics and continuous monitoring by capnography or impedance tomography are the basis for decision making.

In our clinical practice [17] all this should be included in a unit protocol that minimizes variability among professionals and ensures continuity of care. The protocol should also include as important aspects the high qualification of the nursing staff to avoid infections, respiratory physiotherapy, humanization and follow-up after discharge from ICU.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Update in SARS-CoV-2 pneumonia

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Steroid therapy and antiviral treatment in SARS-CoV-2 pneumonia: clinical contexts and indications

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ABSTRACT

Critically ill patients with COVID-19 face a higher risk of disease progression and complications. The current standard of care includes supportive care measures and fluid management. The Recovery trial observed a reduction in all-cause, 28-day mortality (p<0.001) when patients with COVID-19 requiring oxygen therapy received 6 mg of dexamethasone per day for 10 days. In contrast, in patients not requiring oxygen, no benefit was observed: 28-day mortality rates for the dexamethasone and routine care groups were 17.8% and 14%, respectively. To corroborate these results, the World Health Organization (WHO) performed a meta-analysis. The study showed that the use of systemic corticosteroids compared with routine care placebo was associated with a decrease in all-cause, 28-day mortality. With respect to the effectiveness of remdesivir, the ACTT-1 trial found that the drug conferred a benefit on time to clinical improvement. The subgroup analysis in the clinical trial also showed a benefit per mortality in patients requiring supplemental oxygen, albeit not those in need of mechanical ventilation.

Keywords: corticosteroids, antivirals, COVID-19, severe diseases

INTRODUCTION

The COVID-19 pandemic continues to cause substantial impact globally. By January 25th, 2022, more than 349 million confirmed cases had been reported and more than 5.5 million people had died. People with pre-existing comorbidities and elderly individuals comprise the most vulnerable populations of the respiratory disease. Indeed, COVID-19 is complex, with critically ill patients facing a higher risk of progression to severe disease and multisystem complications. In the former, the cause is viral replication; in the latter, the systemic effects result from the host immune response to the virus.

Currently, for hospitalized patients with COVID-19, the standard of care includes supportive care measures for the most frequent complications, i.e., pneumonia, acute respiratory distress syndrome, sepsis and septic shock. These complications have been related to higher rates of mortality.

At the beginning of the pandemic, there was no substantial evidence to support a specific treatment strategy for COVID-19, especially in severe cases. The lack of strong evidence, therefore, resulted in the use of several medications, including antivirals and antimalarials. More specifically, clinicians began administering corticosteroids as adjunct treatment in patients with severe COVID-19. Clinical experience acquired from corticosteroid use in severe community-acquired pneumonia (CAP) suggested that lower doses of corticosteroids for a short duration appeared to decrease mortality in severe CAP and in moderate-severe acute respiratory distress syndrome (ARDS) [1]. However, given past reports of corticosteroid use in cases of severe influenza pneumonia and Middle East Respiratory Syndrome (MERS), administration of such drugs were not recommended to treat COVID-19 at the beginning of the pandemic [2].

There is still a debate about both the effectiveness of antivirals such as remdesivir and indications for systemic corticosteroids in critically ill patients with COVID-19.

COVID-19 SPECTRUM: SEVERITY, DISEASE PATHOGENESIS AND POSSIBLE TREATMENT

We can distinguish five stages of severity in COVID-19: **Asymptomatic,** in which a patient tests positive for SARS-CoV-2 but does not present any symptoms; **Mild illness, in which** mild symptoms such as fever, cough and changes in

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Table 1 Experience with corticosteroids

Study	Relevant outcomes
RECOVERY trial 4,321 Hospitalized patients [12]	The use of 6 mg of dexamethasone per day for 10 days in patients with COVID-19 requiring oxygen therapy resulted in a reduction in all-cause, 28-day mortality (p<0.001). In patients not requiring oxygen, no benefit was observed: 28-day mortality rates were 17.8% and 14% for the dexamethasone and routine care groups, respectively.
WHO prospective meta-analysis of clinical trials 1,703 Critically ill patients [13]	The administration of corticosteroids was associated with lower all-cause, 28-day mortality, compared with routine care or placebo,
Propensity score matching analysis including 409 with severe COVID-19 related to ARDS [14]	Corticosteroid use was associated with a higher 28-day mortality rate and a delay in SARS-CoV-2 RNA clearance.
A systemic review and meta-analysis 20,197 patients with COVID-19 requiring either oxygen therapy or mechanical ventilation [23]	A beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation were reported.
A single pretest, single posttest quasi-experiment study 213 moderate to severe COVID-19 [24]	An early short course of methylprednisolone in moderate to severe COVID-19 showed a reduction in escalation of care and improved clinical outcomes.
A prospective, multicenter and observational cohort study in critically ill adult patients with COVID-19 691 patients [25]	Early use of corticosteroids in critically ill patients with COVID-19 was associated with lower mortality than delayed use.

taste/smell appear, albeit not dyspnea; **Moderate illness, in which** a patient presents an oxygen saturation level >=94% and lower respiratory tract disease; **Severe illness, in which** a patient presents an oxygen saturation level <94%, respiratory rate >30/min, and lung infiltrates >50%; and, **Critical illness,** in which a patient presents respiratory failure, shock, and multi-organ dysfunction or failure [3].

Viral replication is higher within the initial stages of COVID-19 yet lower in the more severe forms. Inflammation is, however, prominent in moderate to severe COVID-19, persisting into the critical phase of the disease. Similarly, hypercoagulability is related to severe and critical stages of COVID-19. Given such understandings, recommendations for COVID-19 therapy include antivirals during early stages of COVID-19—being the most effective when viral replication is higher—and anti-inflammatory agents for those patients with severe and critical forms of COVID-19 [4].

EXPERIENCE OF CORTICOSTEROID USE IN SEVERE LUNG INFECTIONS AND COVID-19

Severe lung infections may result in illnesses capable of causing pneumonia and acute respiratory failure. In the latter case, it could progress rapidly to ARDS, which is related to worse outcomes. This association is partly due to inflammation that can increase the risk of sepsis and septic shock, especially in individuals with a higher likelihood of infection, like the elderly orthose with comorbidities, e.g., diabetes mellitus or chronic respiratory or cardiovascular diseases [5]. It is important to remark that co-infection, especially in the case of viral pneumonia with bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, are also related to worse outcomes. In severe CAP, the use of adjunct therapy with corticosteroids—a potent inhibitor of the immune response—has shown to reduce the incidence of treatment failure and shorten the time to clinical stability [1]. However, no reduction in mortality has been demonstrated to date. Instead, there are studies that report an increase in hospital readmission and complications such as hyperglycemia [6]. Current IDSA/ATS CAP guidelines do not recommend the use of corticosteroids in routine clinical care [7]. Yet, its use is suggested in patients with CAP who either present septic shock or require mechanical ventilation due to respiratory failure primarily caused by pneumonia.

Regarding the use of corticosteroids as adjunct therapy for influenza pneumonia, strong evidence from several systematic reviews and meta-analyses show a relationship between the administration of such drugs and higher mortality rates [8]. A meta-analysis that evaluated 10 trials (6,548 patients with influenza pneumonia) reported that the mortality risk ratio was 1.75 for patients who received corticosteroids [9]. There was a reporting of similar results when only patients with influenza virus H1N1 were analyzed (RR 1.61). The authors also described that patients who received corticosteroids had longer intensive care unit (ICU) length of stay (median difference 2.14 days) compared to those patients who did not. Another systematic review and meta-analysis that included 15 studies (6,427 patients) showed that corticosteroids were associated with both higher mortality (OR 1.53) and incidence of nosocomial infections (OR 3.15) in patients with severe pneumonia and ARDS [10]. Current ATS/IDSA guidelines recommend not to use corticosteroids routinely in adults with severe influenza pneumonia (this is a conditional recommendation with low-quality evidence)[7]. Furthermore, current guidelines

Table 2 Experience with remdesivir

Study	Relevant outcomes
ACTT-1 trial: 1,062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo) [26]	Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), while those who received placebo had a median recovery time of 15 days (95% CI, 13 to 18) Mortality rates were 6.7% (remdesivir) and 11.9% (placebo) by day 15 and 11.4% (remdesivir) and 15.2% (placebo) by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of 532 patients receiving remdesivir (24.6%) and in 163 of 516 patients receiving placebo (31.6%).
SOLIDARITY trial: 11,330 adults underwent randomization: 2,750 were assigned to receive remdesivir; 954, hydroxychloroquine; 1,411, lopinavir (without interferon); 2,063, interferon (including 651, interferon plus lopinavir); and 4,088, no trial drug [20]	Death occurred in 301 of 2,743 patients receiving remdesivir and in 303 of 2,708 receiving the control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P = 0.50). Ventilation was initiated after randomization in 295 patients receiving remdesivir and in 284 receiving the control. A small effect of remdesivir on time to recovery was observed. No mortality benefit was reported.
Prospective, controlled and non-randomized study: 151 patients with COVID-19 requiring supplemental oxygen therapy were enrolled (76 in the remdesivir/dexamethasone group, and 76 in the dexamethasone group) [21]	Faster viral clearance occurred in the remdesivir/dexamethasone group compared to the dexamethasone group (median 6 vs 16 days; p<0.001). 30-day mortality in the remdesivir/dexamethasone group was 1.3%; however, the rate was 16% in the dexamethasone group (p<0.005). There was a reduction in hospitalization days in the remdesivir/dexamethasone group, compared to the dexamethasone group (p<0.0001)

discourage the systematic use of systemic corticosteroids in cases of influenza infection.

Excessive inflammatory responses were observed in patients with severe COVID-19. Fatal ARDS—as a result of such inflammation--was related to excessive mortality. The inflammatory cytokine storm observed in severe cases were associated with an increased production of pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6 and tumor necrosis factor alpha (TNF-α) [11]. Using corticosteroids was a good option to modulate the immune response to the viral infection. However, without the necessary clinical evidence about their use, the debate on the topic remains active. The RECOVERY trial [12] that included 4,321 hospitalized patients with COVID-19 found that the use of 6 mg of dexamethasone per day for 10 days in patients with COVID-19 requiring oxygen therapy resulted in a reduction in all-cause, 28-day mortality (p<0.001). In contrast, in patients not requiring oxygen, no benefit was observed: 28-day mortality rates for the dexamethasone and routine care groups were 17.8% and 14%, respectively. These results demonstrated that the use of dexamethasone decreased mortality in patients with COVID-19 requiring oxygen therapy, irrespective of the mode of ventilation (invasive or non-invasive). After the RECOVERY trial, the World Health Organization (WHO) carried out a prospective meta-analysis of clinical trials including critically ill patients with COVID-19. The stud confirmed the results obtained during the RECOVERY trial, showing that the use of systemic corticosteroids compared with routine care placebo was associated with a reduction in all-cause, 28-day mortality [13] (Table 1). Interestingly, in a propensity score matching analysis that evaluated corticosteroid use in patients with severe COVID-19-related ARDS, the authors reported that the use of corticosteroids was associated with increased mortality and delayed viral clearance [14]. A subsequent editorial to the previous article proposed that treatment timing, dosage and severity of COVID-19 could determine the immune response and viral clearance. The authors stated that the use of corticosteroids in an early stage of the infection could be harmful for the patient: it could suppress the host antiviral activity and would allow for viral replication, causing cytopathic damage to the alveolar epithelial cells. On the contrary, though, the use of corticosteroids in patients after their immune system has controlled viral replication could prove beneficial. Such drug administration could contribute to reducing pro-inflammatory cytokines, enhancing anti-inflammatory cytokines, decreasing lung vascular permeability, improving epithelial barrier integrity and promoting alveolar edema fluid clearance [15].

Administering an early short course of methylprednisolone in moderate to severe COVID-19 showed a reduction in escalation of care and improved clinical outcomes. Also, when compared to delayed use, the early use of corticosteroids in critically ill patients with COVID-19 was associated with low-

er mortality. Finally, a beneficial effect of corticosteroids on short-term mortality and a decreased need for mechanical ventilation was reported (Table 1). The European Respiratory Society living guidelines recommended the use of corticosteroids only for patients with hypoxemic respiratory failure requiring oxygen administration[16]. The current National Institutes of Health (NIH) guidelines for COVID-19 therapy recommended the use of systemic corticosteroids in patients requiring supplemental oxygen. Disease severity of patients determined the use of dexamethasone alone or in combination with either remdesivir or a secondary immunomodulator such as tocilizumab or baricitinib [17]. The RECOVERY trial found that adding tocilizumab to dexamethasone had a beneficial impact on mortality in hospitalized patients with COVID-19, hypoxia and systemic inflammation, compared to routine care alone [18].

All of these data supported the recommendation for the use of corticosteroids, especially in critically ill patients with COVID-19 requiring oxygen therapy, and highlighted the beneficial effect of the association between such use and tocilizumab. However, there are some questions that warrant further investigation, including defining the required dosage and early use of corticosteroids; and understanding the effect of corticosteroid use on viral clearance and the possible long-term benefits in pulmonary sequelae.

HOW DOES REMDESIVIR CONTRIBUTE TO COVID-19 MANAGEMENT?

Remdesivir is a broad-spectrum antiviral capable of inhibiting the RNA polymerase and disrupting various stages of viral growth. Remdesivir received emergency approval after data had demonstrated its efficacy in reducing disease progression and severity, thereby resulting in shorter hospitalization time. However, there is controversary regarding the antiviral's beneficial effects. The effectiveness of remdesivir was evaluated in large randomized controlled trials (RCT). The ACTT-1 trial [19] showed a reduction in time to clinical improvement, while the subgroup analysis demonstrated a mortality benefit in patients requiring supplemental oxygen, albeit not those patients in need of mechanical ventilation. However, the SOLIDARITY trial [20] showed no mortality benefit with the use of remdesivir. In a separate prospective, controlled and non-randomized study [21] investigators evaluated the effectiveness of remdesivir with dexamethasone against dexamethasone alone in patients with COVID-19 requiring supplemental oxygen therapy. The study included 151 patients (76 patients in the remdesivir/dexamethasone group and 75 in the group receiving only dexamethasone). The authors showed that there was a significant reduction in mortality and length of hospitalization clearance in the group of patients who received remdesivir with dexamethasone compared with the group who received dexamethasone alone (Table 2). Furthermore, SARS-CoV-2 clearance was faster in the former group compared to the latter.

The latest WHO living guidelines [22] do not recommend the use of remdesivir in patients with COVID-19, irrespective of disease severity. Also, the ERS living guidelines do not recommend the use of remdesivir in patients who require invasive mechanical ventilation. The NIH therapeutic guidelines recommend the use of this antiviral in hospitalized patients requiring oxygen supplementation yet not for those in need of mechanical ventilation.

CONCLUSIONS

Despite the rapid increase in scientific evidence on several different molecules related to treatment and COVID-19 disease stages, more data and findings are necessary to improve the overall clinical management. This statement holds especially true for those patients in critical condition. The general recommendation to treat patients with COVID-19 must depend on disease severity and the host's immune response to the viral infection. Antiviral therapy has been demostrated to confer a beneficial effect if administered during the early stages of the disease when viral replication is higher. Corticosteroids has a great beneficial impact in severe and critical cases of COVID-19 given the excessive inflamation.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Update in SARS-CoV-2 pneumonia

Immune treatment in COVID-19

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ABSTRACT

Current immune treatment directed to avoid viral replication relies mainly in convalescent plasma and monoclonal antibodies (mAbs). No clinical benefit for convalescent plasma has been reported in a meta-analysis and systematic review compared to standard of care. MAbs are recombinant proteins capable to bind with SARS-CoV-2 preventing its entrance into cells. Several mAbs have shown reduction in viral load and/or progression of the disease such as casirivimab-imdevimab, bamlanivimab-etesevimab and sotrovimab. After the apparition of Omicron variant, it has been reported that sotrovimab retained its activity whereas the other two combinations exhibited loss of neutralizing activity. Several aspects as the target population, timing and doses, serological patient status and evolution of variants still require attention, monitorization and further studies for knowledge gaps.

Key words: monoclonal antibodies, S protein, SARS-CoV-2

INTRODUCTION

During the whole pandemic and the successive waves some differences among the patient profile have been reported. Nevertheless, it was rather constant that patients with immunosuppression, elderly and those with several risk factors for progression are still a vulnerable group with difficulties to mount an effective immune response causing a challenge for treatment (Table 1). For so, despite the high proportion of vaccinated, health resources are still compromised and a large amount of people would require hospitalization and even admission to ICU [1]. Concerning the microorganism it is crucial for clinical course and outcome the viral load and persistence of replication therefore a treatment directed to avoid viruses entering into cells host constitutes a new approach. In that clinical scenario, the ability to provide an immune treatment is a logical and attractive option. The two most studied options are: convalescent plasma and monoclonal antibodies (mAbs).

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CONVALESCENT PLASMA

In a randomized trial performed, Estcourt [2] evaluated in two arms (convalescent plasma vs. Placebo) in critically ill patients. The primary ordinal end point was organ support-free days (days alive and free of intensive care unit-based organ support) up to day 21. The results showed neither no differences for primary outcome nor for mortality that was very high in the two arms (37.3% vs 38.4%). Janiaud et al [3] in a systematic review including 1060 patients from 4 peer-reviewed RCTs and 10,722 patients from 6 other publicly available RCTs. They concluded that convalescent plasma showed no benefit for all-cause of mortality and other outcomes as deterioration or requirement of mechanical ventilation.

MONOCLONAL ANTIBODIES

Neutralizing monoclonal antibodies (mAbs) against SARS-CoV-2 are recombinant proteins obtained from B cells of patients or humanized mice. MAbs can be produced by different methods and constitute a method to provide passive immunization to patients. They act binding to virus and avoiding its fusion with ACE receptor – found on cells in the respiratory system, gastrointestinal tract and endothelium- neutralizing its capacity to enter into the host 'cells. The primary antigenic epitope on SARS-CoV and SARS-CoV-2 is the S protein and specifically receptor-binding domain (RBD) in most of them. Moreover, after binding with viruses facilitate the cellular phagocytosis and antibody-dependent cellular cytotoxicity directly or in infected cells promoting eventually their apoptosis [4]. A potential problem is that mAbs might cause damage through antibody-dependent enhancement of inflammation or viral replication.

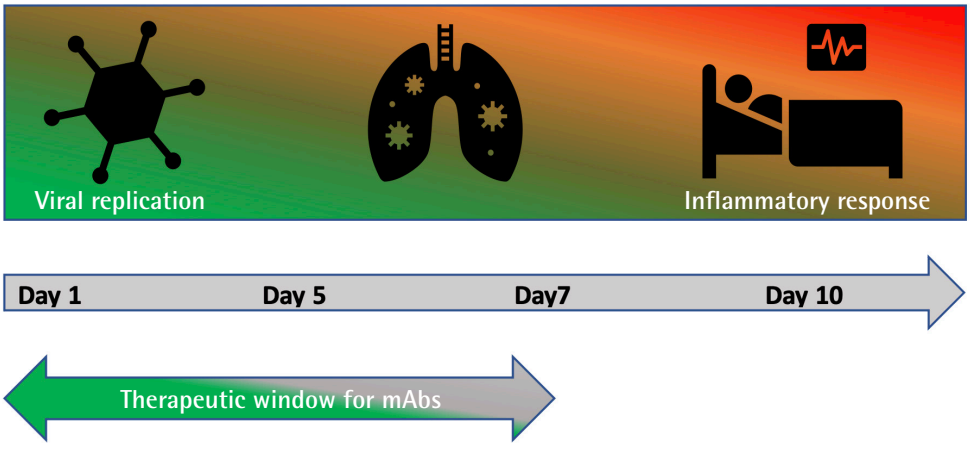

Figure 1 | **Graph representing the two phases -viral and inflammatory- in COVID-19 disease.**

Due to their action mechanism mAbs as neutralizing antibodies are capable to reduce viral load when given in the early phase of viral replication precluding a disease progression through a clearance of viruses (Figure 1). The FDA, in United States and the EMA, in European countries have issued advice for the use of several mAbs, bamlanivimab and etesevimab, casirivimab and imdevimab (REGN-COV2) in outpatients who are not needing supplemental oxygen and who are at high risk of progressing severe COVID-19 and, lately, sotrovimab. The concern regarding mAbs from the initial studies was the potential loss of activity with the apparition of new variants with mutations precluding its binding to the S protein with the subsequent absence of efficacy [5].

Bamlanivimab and etesevimab. They are two humanized Ig G1 neutralizing antibodies that act against RBD. bamlanivimab-etesevimab bind to distinct although overlapping epitopes. In February 2021, Gotblier et al [6] compared the efficacy of bamlanivimab in monotherapy with different doses, or in combination with etesevimab and versus placebo in outpatients with mild or moderate COVID-19 (Blaze 1 study) to reduce viral virus load. Treatment was initiated within 3 days of SARS-CoV-2 positive test. They found that combination therapy, but not bamlanivimab monotherapy, resulted in a decrease in SARS-CoV-2 log viral load at day 11.

In July 2021, Dougan et al. [7] in a randomized 1:1 phase III trial performed in adolescent and adult nonhospitalized patients with mild infection and with at least one risk factor for progression, compared one infusion of mAbs (2,800 mg of bamlanivimab and 2,800 mg of etesevimab) vs. placebo. Treatment was administered within the first 4 days from onset symptoms and patients had a median Ct (cycle-threshold) of 23.9 the day of infusion. They found a significant lower hospitalizations and deaths at day 28 in the arm of treatment (70% reduction) and a rapid decline of viral load at day 11. During the trial, variants Beta o gamma were not observed. Posterior studies have shown that some circulating viral variants, such beta and gamma variant have *in vitro* resistance to bamlanivimab plus etesevimab and it has been shown that is not active against Omicron variant [8].

Casirivimab and imdevimab (REGEN-COV2). REGEN-COV2 [9] is a combination of two neutralizing mAbs, casirivimab and imdevimab, formed with IgG1 with unmodified Fc regions that bind two distinct epitopes sites on RBD. In animal models, the combination reduced the viral load and the apparition of lung severe disease. Weinreich et al, in a phase III trial performed in outpatients with risk factors for progression, compared two different REGEN-COV iv doses (2,400 mg-1,200 mg casirivimab and 1,200 imdevimab- or 8,000 mg-4,000 mg of each) versus placebo. Patients were randomized to receive one of the two doses or placebo. This trial showed that REGEN-COV2 is associated with clinical benefit, regardless of baseline serum antibody status, so that serologic testing at the time of the COVID-19 diagnosis is less critical for making clinical treatment decisions. Both the 1,200 mg and 2,400 mg doses of REGEN-COV2 exhibited similar antiviral and clinical efficacy suggesting that REGEN-COV2 concentrations were above the minimally effective dose. Regarding adverse events, they reported low incidences of serious events, hypersensitivity reactions, and infusion-related reactions.

Noteworthy, the study revealed an association between the baseline viral load and COVID-19–related hospitalization or death in the placebo arm. In fact, seronegative antibody patients in the placebo group had higher median viral loads at baseline than those who were positive.

The 2,400 mg dose of REGEN-COV2 received an emergency use authorization from the FDA (Food and Drug Administration) in November 2020 for the treatment of high-risk outpatients with mild-to-moderate COVID-19. In June 2021, after this trial showed that the 1,200 mg dose provided a similar

Table 1 Eligible candidates for mAbs considering age ≥12 years and weight ≥40 Kg

Age	≥65 years
Immunosuppressed patients	Active treatment for solid tumor and hematologic malignancies
	Receipt of solid-organ transplant and taking immunosuppressive therapy
	Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant
	Moderate or severe primary immunodeficiency
	Advanced or untreated HIV infection
	Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive.
Chronic conditions	Cardiovascular disease and/or Hypertension
	Chronic renal disease
	Respiratory chronic conditions
	Cystic fibrosis
	Neurological conditions
	Sickle cell disease
Obesity	BMI >35
	Overweight > percentile 85
Technology dependence	Tracheostomy, non-invasive ventilation

decrease in the risk of hospitalization or death and a virologic efficacy that was similar to that provided by the 2,400 mg dose, the 1,200 mg dose received an EUA (replacing the 2,400 mg dose).

In the Recovery study [10] in hospitalized patients treated with REGEN-COV2 versus standard of care, the results showed that there was only a beneficial effect, reducing mortality at day 28, in those seronegative patients compared to those seropositive.

REGEN-COV2 combination antibody therapy showed efficacy in vitro against several circulating variants of concern and variants of interest, including alpha, beta, delta, and gamma but not against Omicron variant.

Sotrovimab. It was identified by screening antibodies from a patient who had been infected during the 2003 SARS-CoV-1 outbreak. The advantage is its ability to also neutralise SARS-CoV-2 because its binding site is a highly conserved pan-sarbecovirus epitope of the SARS-CoV and SARS-CoV-2 spike protein outside the RBD motif. Due to this different and more conserved binding site, its ability to neutralise SARS-CoV-2 implies that mutational escape from different variants is more difficult. The Fc portion of the parent antibody has been modified to extend sotrovimab's half-life to around 49 days. It is given as a single intravenous dose and it has been well tolerated in clinical studies, although occasional serious hypersensitivity reactions have occurred.

Gupta et al in the Comet-Ice study [11] have evaluated the parental form of sotrovimab in a multicenter, double-blind, phase 3 trial, nonhospitalized patients. The study recruited patients with symptomatic COVID-19 (≤5 days after the onset of symptoms) and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo (in a 1:1 ratio). The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death within 29 days after randomization. The population study was comprised by 583 patients (291 in the sotrovimab group and 292 in the placebo group) and most patients have at least 1 risk factor for progression of the disease. The mean age 53 years and 59% of them treatment was initiated within the three days from onset of symptoms. They found that 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction, 85%; 97.24% confidence interval, 44 to 96; P = 0.002).

Evidence in hospitalised patients is more limited, and the sotrovimab arm of ACTIV-3 was stopped due to futility after recruiting 344 participants, although no safety concerns were raised. TICO study [12], is a randomized study to compared sotrovimab 500 and a combination of BRII-196 1000 mg plus BRII-198 1,000 mg, in hospitalized patients.

The primary outcome was time to sustained clinical recovery, defined as hospital discharge and remaining at home for 14 consecutive days. Patients included in the study were receiving treatment with Remdesivir and corticosteroids

Table 2 Parameters and its punctuation included in the Mass score for prioritize mAbs therapy [15]

	Punctuation
Age > 65 years	1
BMI >35	1
Diabetes	2
Renal chronic disease	3
Cardiovascular chronic disease >55 years	2
COPD >55 years	2
Hypertension >55 years	1
Immunosuppressed patient	3

(around 60%) and the median of days from symptoms onset was 8 days. Patients included different severity (42-45% were receiving O2 <4l/min) and around 58% were seronegative. The results showed no benefit in the arm of sotrovimab. Noteworthy, an important consideration is that the additional antiviral activity from mAbs is not providing incremental benefit in a population treated with remdesivir and corticosteroids.

The appearance of the Omicron has forced to revaluate the activity of the mAbs against this new variant. Touret et al [8] in a preprint showed that sotrovimab maintained activity against Omicron whereas the others exhibited loss of neutralising activity https://covdb.stanford.edu/page/susceptibility-data/).

Tixagevimab and cilgavimab. This new long-acting combination mAbs has been authorized for the FDA in USA for pre-exposure prophylaxis proving a new therapeutic approach to avoid the acquisition of the infection [13]. This strategy aims to act in a particularly vulnerable population, such as all those unable to mount an immune response due to pre-existing conditions such as immunocompromised due to transplant or biological treatments. That combination has sought emergency use authorization in USA after demonstration if a phase III trial that it was capable to reduce the risk of COVID-19 symptoms by 77% [14]. It is administrated intramuscularly making the treatment more suitable than intravenous administration.

CURRENT RECOMMENDATIONS

The current recommendations for indication and prioritization of mAbs depend mainly in three pillars: 1- identification of patient at-risk for developing severe episode 2- timing is crucial to provide treatment within the first 5 days preferably 3. Serological status of patients as it has been reported better favorable outcome in those seronegatives. Several comorbidities and diseases are considered by FDA and EMA (Table 1). Considering prioritization of patients, an score formed with different clinical conditions and age has been proposed (Mass score) (Table 2) to estimate the number needed to treat in relation with number of comorbidities [15]. The requisite is the activity of mAbs against the circulate variants.

The challenge for recommendations is the continuous change of COVID-19 pandemics and the new variants. Nevertheless, National Institutes of Health (NIH) indicates mAbs treatment both in pre-exposure and post-exposure in the outpatient (https://www.covid19treatmentguidelines.nih.gov). The target population are those with high risk of progression or developing severe episode if they get infected. In post-exposure NIH recommends against the use of the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab because they have markedly reduced susceptibility to Omicron, which is currently the dominant SARS-CoV-2 variant. If Omicron variant is suspected or if its prevalence is very high, NIH recommends the use of Sotrovimab.

For hospitalized patients, Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19. Nevertheless, through expanded access programs the products may be available for patients who either have not developed an antibody response to SARS-CoV-2 infection. In Spain, AEMPS https://www.aemps.gob.es/ allows their use in immunosuppressed patients with seronegative patients

FINAL COMMENTS

In summary, concerning passive immunization mAbs constitute an option for early treatment as they prevent entering viruses into cells mainly directed to patients at higher risk for severe episodes and/or unable to mount and adequate immune response. The main concern is the capacity of new variants to escape from their action [16]. There are several challenges: rapid identification of most vulnerable patients, logistic consideration for endovenous administration and the question of the patient 'serologic status. For prioritization of potential candidates a fast serologic tests is required to determine if patients are seronegative or the amount of Ig G antibodies is low.

There are still several gaps of knowledge mainly in immunosuppressed patients and unanswered questions regarding the evolution of variants of concern, their efficacy, the ideal dosages or mAbs combinations and if there is a threshold point of host Ig G antibodies useful for better personalizing indications.

The near future apparition of oral antiviral will modulate how to prioritize the indications of mAbs versus other alternative oral treatments.

CONFLICTS OF INTEREST

Rosario Menéndez: Advisory Board and honorarium for educational collaboration in talks and courses for GSK. Rest of authors: none to declare

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Update in SARS-CoV-2 pneumonia

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Respiratory infections in Coronavirus disease 2019

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ABSTRACT

In the last two years, the capacity of our hospitals has clearly been overwhelmed due to the COVID-19 pandemic The patient who comes to the hospital with a respiratory coinfection does not have the same characteristics as the patient who suffers a superinfection while hospitalized. The number of secondary infections increase proportionally to the severity of the patient's disease. Besides, pathogens that cause a coinfection are clearly differentiated from the pathogens that cause a superinfection. However, in patients subjected to airway manipulation, superinfections by distinct pathogens can occur. Seventy five percent of patients admitted worldwide with COVID-19 (especially during the first two waves of the pandemic) received some form of antibiotic treatment during admission. In this context, it is essential to develop and implement algorithms that allow us to define the predictors in each individual case for the development of a superinfection

Key words: Coronavirus disease 2019; Coinfection; Superinfection; Rational antimicrobial use

INTRODUCTION

In the last two years, the capacity of our hospitals has clearly been overwhelmed due to the COVID-19 pandemic. This has meant that inpatient care has changed dramatically. The increase in the number of patients hospitalized with pneumonia caused by SARS-CoV-2, together with the comorbidities that these patients present, has clearly increased the risk of suffering a superinfection during admission [1]. Most of the published literature does not distinguish between COVID-19 patients with a coinfection or a superinfection. According to the CDC definitions, the difference between both entities lies in their temporality. A coinfection is an infection that appears concurrently with SARS-CoV-2 infection, while a superinfection is one that occurs days later in a patient diagnosed with COVID-19. In other words, the difference between the two entities is temporal and this fact has implications that are important from a diagnostic and therapeutic point of view [2].

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PATHOPHYSIOLOGY OF SUPERINFECTION IN COVID-19

The primary function of the respiratory system of gas exchange renders it vulnerable to environmental pathogens that circulate in the air. Physical and cellular barriers of the respiratory tract mucosal surface utilize a variety of strategies to obstruct microbe entry. It is well known that certain respiratory infections caused by viruses, such as influenza virus infection, eventually damage the respiratory epithelium and result in decreased mucociliary clearance, increased bacterial receptor cell surface area, and intercellular junction incompetence. These facts, combined with an impaired immune response due to the functional damage of macrophages and neutrophils, together with a deregulated cytokine response, produce a modification of the microenvironment that ends up creating a perfect niche for secondary infections [3]. In the case of influenza, secondary bacterial pneumonias caused by *Streptococcus pneumoniae* or *Staphylococcus aureus* are well described in the literature.

Several reviews have evaluated the pathophysiology of coinfection in patients diagnosed with SARS-CoV-2 pneumonia [4]. In this regard, we can distinguish two periods in the pathogenesis of SARS-CoV-2 pneumonia. In the initial stages of pneumonia, infection of bronchial epithelial cells and type I and II alveolar pneumocytes, as well as infection of capillary endothelial cells occurs. This is followed by a local inflammatory response with recruitment of lymphocytes, monocytes, neutrophils, and macrophages. This cytological response is accompanied by a massive release of cytokines that triggers the

second phase in SARS-CoV-2 pneumonia. In this second phase, because of a continued inflammatory response, there is thickening of the alveolar-capillary space, with increased vascular permeability leading to the formation of hyaline membranes. At the endothelial level, coagulation is activated leading to microthrombus formation and other phenomena related to thrombo-inflammation. All these factors contribute to create a perfect microenvironment that leaves the pulmonary alveolus in a perfect situation for other pathogens invasion, whether viral, bacterial or fungal, to adhere to this damaged alveolar epithelium, multiply and generate a secondary infection [5].

SUPERINFECTION BURDEN IN COVID-19

A recently published study analyzes the risk factors and characteristics of infections occurring in critically ill patients diagnosed with COVID-19 [6]. This study does not differentiate between coinfection and superinfection. Thirty-eight patients were included, 58% of whom developed a secondary infection, with respiratory infections being the most frequent, followed by bacteremia and urinary tract infections. According to a meta-analysis published by Langford, where a distinction is made between coinfections and superinfections, 3.5% of patients admitted due to COVID-19 suffer a bacterial coinfection, with 14.3% of patients suffering a bacterial superinfection during admission [7]. In a multicenter study published by Feng [8], the number of secondary infections increased proportionally to the severity of the patient's disease. In this study, 4% of patients with moderate disease, 8.3% of patients with severe disease, and up to 34% of critical patients are diagnosed with a superinfection during admission.

Regarding to the etiology of these infections, Westblade et al. showed that pathogens that cause a coinfection are clearly differentiated from the bacterial pathogens that cause a superinfection [9]. Bacterial coinfections are dominated by community pathogens such as *S. pneumoniae* or *Haemophilus influenzae*, while superinfections occurring after admission are dominated by hospital pathogens such as enterococci, *Pseudomonas aeruginosa*, *S.s aureus* and *Enterobacter* species. The pathogens most frequently isolated in a study [6] were Gram-negative bacilli in 50%, followed by Gram-positive cocci in 25%. It should be noted that 11% of patients had a secondary viral infection and almost 8% had a secondary fungal infection. These secondary infections were associated with an increase in the average length of stay and in the mortality rate. Interestingly, in this study, the rate of respiratory infections was 90% in patients undergoing tracheotomy, 30% in patients undergoing mechanical ventilation and 12% in patients undergoing non-invasive mechanical ventilation techniques.

It should be considered that sometimes, and especially in patients subjected to airway manipulation, superinfections by distinct pathogens can occur. In a paper published by Zhang et al [6] in which they study the time of appearance of secondary respiratory infections after different types of respiratory support, they describe how after a tracheotomy the mean time until the appearance of a superinfection is 9 days, with a range of 31 different pathogens being observed in this type of infection. After tracheal intubation, the mean time to the appearance of an infection was 4.5 days, with a smaller range of pathogens, and the mean time to the appearance of a secondary superinfection after the use of noninvasive ventilator support, the mean time was 7.5 days, with a lower diversity of pathogens than in the other 2 situations.

As it has been described in several studies, patients with COVID-19 pneumonia are patients at special risk of suffering secondary invasive fungal infections, as occurs in the case of other viral pneumonias such as pneumonias caused by the influenza virus [10]. Patients with COVID-19 pneumonia, especially those patients in critical care units, and who have undergone treatment with corticosteroids and other immunosuppressants such as interleukin inhibitors, and have also undergone broad-spectrum antibiotic treatment, are patients who are particularly predisposed to fungal superinfection, especially by *Aspergillus* species or, as has been described in some countries, by *Mucor* species.

RISK FACTORS AND IMPACT OF SUPERINFECTIONS

Several studies have evaluated the risk factors that predispose to a superinfection in patients with COVID-19 pneumonia. In the study by Ripa et al. for example, the longer the duration of hospitalization, the greater the probability of superinfection [11] The percentage of patients who suffer a superinfection after 7 days of admission is 2%, while in patients with stays of 29 days, the percentage of infections rises to 16%. The absolute number of lymphocytes is another factor that has been described in several studies as a predictor of secondary superinfection. The patients at greatest risk would be those with counts below 0.7×10^9/L. In patients subjected to mechanical ventilation, PaO2/FiO2 < 200 is a well-established risk factor for secondary superinfection. Regarding the impact of these superinfections on the patient's evolution and average length of stay, it has been well demonstrated that patients who suffer a superinfection during the course of COVID-19 significantly prolong their average length of stay when compared to those who do not suffer a secondary infection, and are also more likely to die than those who do not have a secondary infection [6].

COVID-19 AND ANTIMICROBIAL USE

Langford's meta-analysis, described how 74% of patients admitted worldwide (especially during the first two waves of the pandemic) with COVID-19 received some form of antibiotic treatment during admission [12]. These figures were very stable across WHO regions. If we stratify patients by age, up to 83% of adults received antibiotic treatment during admission, while only 40% of children do. Similarly, if we stratify by place of patient care, up to 86% of patients admitted to the ICU received antibiotic treatment at some time during admission, 74% of patients admitted to a conventional hospital ward received antibiotic treatment and, surprisingly, up to 60% of

patients treated on an outpatient basis received some type of antibiotic treatment. In this same meta-analysis and for the different WHO regions, the most used families of antibiotics were quinolones, and macrolides, followed by beta-lactams combined with beta-lactamase inhibitors and cephalosporins. In this context, we must consider the impact that antimicrobial therapy in these patients has on the microbiota (especially of the gastrointestinal tract). In this sense, there is some work such as that of Zuo, which describes how the dysbiosis caused by antibiotics in COVID-19 patients impacts on the immune response at the lungs, generating a worse respiratory evolution of these patients [13].

In this context, it is essential to develop and implement algorithms that allow us to define the predictors in each individual case for the development of a superinfection for two reasons. The first is to decide in which patients it is prudent to initiate empirical antibiotic treatment because they have a high risk of superinfection, as well as in which patients it is not necessary to initiate preventive antibiotic treatment because they have a low risk of superinfection. In any case, it is necessary to establish good diagnostic protocols, including the possibility of screening for multidrug-resistant bacteria in certain patients to be able to choose the right empirical treatment in case of suspected superinfection. It is equally important to define in which patients' antimicrobials should be used and in which ones an antimicrobial treatment is not indicated. Similarly, it is essential to re-evaluate each patient 48-72 hours after admission, from the point of view of secondary infection, to decide whether it is necessary to continue with antibiotic treatment in patients in whom antibiotic treatment has been started or whether it can be stopped

REMAINING QUESTIONS

- Which clinical features and laboratory tests can reliably identify the small proportion of hospitalized patients with COVID-19 who have bacterial coinfection and who therefore should undergo diagnostic testing for other infections and receive empirical antibacterial therapy?
- Will the prevalence of bacterial coinfection upon hospital admission for COVID-19 change in subsequent waves of the pandemic, particularly with the emergence of new SARS-CoV-2 variants?
- How will the routine use of corticosteroids change the spectrum of hospital acquired bacterial infections in patients requiring prolonged hospitalization for COVID-19?
- How will the increase in COVID-19 patients who require intensive care around the world influence the emergence of multidrug-resistant bacterial infections?

CONFLICTS OF INTEREST

Author declares no conflicts of interest

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Update in SARS-CoV-2 pneumonia

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Respiratory consequences after COVID-19: outcome and treatment

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ABSTRACT

The SARS-CoV-2 (COVID-19) pandemic represents the infection with the highest lethality, but also the one that has caused the most sequelae and multi-organ consequences, especially respiratory, in the last century. Several actions have been required in the field of respiratory and intensive care medicine to reduce mortality and chronicity. The consequences of COVID-19 are multiple and encompass different physical, emotional, organizing, and economic aspects, which will require a multidisciplinary, transversal, and collaborative approach. This review includes the observations and results of published retrospective and prospective studies on post-COVID19 respiratory sequelae, especially after severe pneumonia with associated adult respiratory distress syndrome (ARDS).

Keywords: post-COVID respiratory dysfunction, post-COVID sequalae

INTRODUCTION

The SARS-CoV2 viral infection (COVID-19) is a global threat with hundreds of millions of affected patients worldwide [1]. As global rates for COVID-19 survival have increased, many are wrestling with the long-term sequelae and more interest has grown concerning the prevalence and appropriate management of residual lung disease in survivors of COVID-19. Post-covid19 lung syndrome would be considered if persistent radiological infiltrates and the consequent physiological respiratory deterioration are present for more than 12 weeks after the acute phase, envisioning post-covid lung sequelae if not resolved after 12 months [2,3].

The major cause of death in COVID-19 is the respiratory failure due to adult respiratory distress syndrome (ARDS) after the cytokine storm, with frequent microvascular thrombotic events and multi-organ system failure [1,2]. Around 60% of patients with ARDS induced by the SARS-CoV-2 viral infection improve clinically and radiologically after 2-3 weeks of treatment [4-6]. However, lung recovery is often slow, sometimes with supplemental oxygen required upon returning home [4-6]. In a minority of cases, clinical-radiological signs of pulmonary fibrosis have been observed in the first chest computed tomography (CT) performed after surviving the acute phase [6,7]. The induced lung fibrotic changes usually improve but in a minority of cases progress, which may associate worsening quality of life and increasing mortality risk [7-11]. Persistent inflammatory abnormalities on chest images beyond the acute illness period have been reported in several cohorts, and observational studies have suggested development of pulmonary fibrosis in a subset of patients [2,5,12-16].

Increasing evidence based on prospective post-covid19 follow-up protocols or retrospective cohorts has suggested different forms of post-COVID-19 lung sequelae that require a multidisciplinary approach [9,13]. Dyspnea, anxiety-depression, fatigue, or muscle weakness are frequent post-covid clinical problems that require an individual approach, including rehabilitation, psychological support, neurological and/or respiratory management, depending on patient features [9] (Table 1). The type of predominant post-covid dysfunction the patient may have depends on different factors, such as disease severity and in-hospital complications, age, gender, and patient comorbidities [12]. While most mild to moderate COVID-19 cases improve and present lung recovery over time, those survivors from severe covid19 that required high-flux nasal cannula (HFNC), non-invasive ventilation (NIV) or intubation and mechanical ventilation (IMV) frequently show interstitial lung abnormalities and pulmonary functional impairment over 6 and 12 months [12-15] (Figure 1). In fact, persistent interstitial changes with respiratory physiological impairment have been described as the most frequent sequela in severe COVID-19 pneumonia survivors [12] (Figure 1). Like other types of lung response after ARDS, different factors and mechanisms could be involved in the devel-

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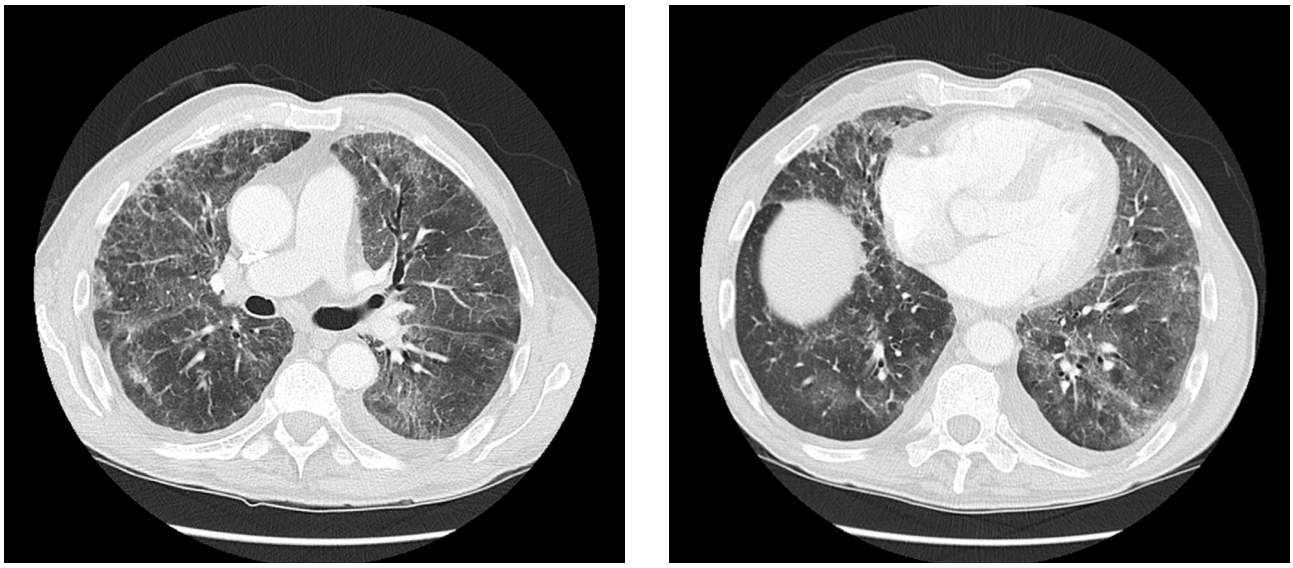
1.A) Thorax high resolution computed tomography (HRCT) shows predominant ground glass opacities, with some reticulation and isolated traction bronchiectasis.



1.B) Thorax HRCT shows predominant fibrotic-like changes; bilateral reticulation and traction bronchiectasis, with lung volume loss, and very limited ground glass opacities.

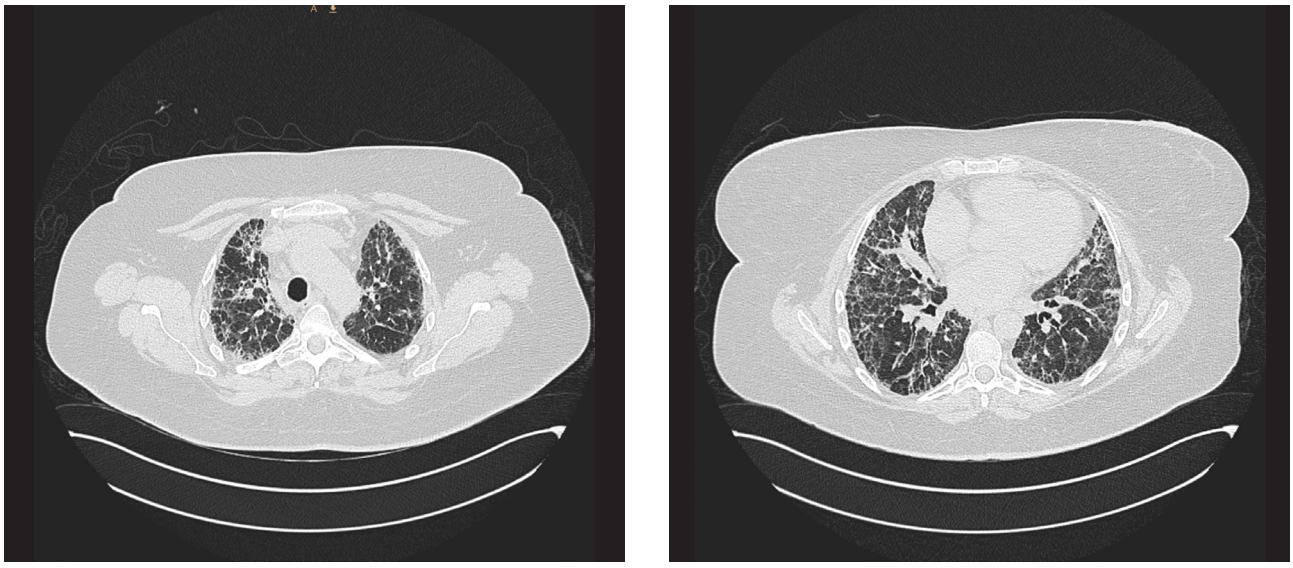


Figure 1 | **Different radiological features of post-covid short-term post-covid lung patients. Here we present two real post-covid cases after 2 months from hospital discharge to differentiate what would be considered "predominant ground glass opacities" versus "predominant fibrotic-like changes".**

opment of post-acute interstitial lung changes and the capacity of repairing *ad integrum* [17,18]. On the other hand, increased risk of pulmonary vascular disease during or after COVID-19 has been also described [19].

Therefore, post- COVID-19 respiratory dysfunction frequently involves muscle, vascular and parenchymal components. Long-term outcomes in different populations are likely to vary.

POST-COVID-19 LUNG SYNDROME: PATIENT FEATURES AND PREDICTIVE FACTORS

Several studies are currently ongoing worldwide to better define what the post-COVID-19 lung syndrome represent. However, to identify those patients with respiratory dysfunction due to persistent lung abnormalities after suffering cov-

id19 pneumonia, optimization of patient follow-up and treatment is necessary [9].

Evidence from previous coronavirus outbreaks - severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) - suggested that persistent respiratory abnormalities were present after severe acute infection [20]. Although long-term studies for SARS and MERS lung sequela were scarce and included a limited number of cases, persistent interstitial changes and pulmonary function deterioration correlated with disease severity, illness duration and age of the patient [20]. Interstitial lung disease (ILD) was reported in 28% at one-year post-SARS and 1.8% at 15-years post-SARS [2,20].

Although several reports analyzing hospitalized COVID-19 cohorts have demonstrated a high incidence of short-term lung interstitial changes with respiratory functional impairment after recovery from the acute phase [2,5,10,11,12-15,21-29], longer follow-up studies on these patients are limited and provide analyzes of no more than one-year [5,21-29]. The proportion of patients with some residual CT abnormality at 2-4 months after hospital discharge ranges from 52% to 85% [5,21-29]. This variability depends in part on the number of patients with severe or critical COVID-19 included in each cohort [2,5,21-29]. Sonnweber, et al showed that post-covid19 survivors improved the mean CT severity score at 3 months follow-up in all cases, but higher score of residual CT changes was present in those severe and critical COVID-19 cases [5]. Furthermore, prospective long-term studies have shown radiological normalization at 1-year CT in most cases that didn't require ventilatory support (IMV, NIV or HFNC) during hospitalization [5,21-29]. Despite the low proportion of cases with interstitial CT abnormalities at 12 months (5-24%), most of them had presented severe or critical COVID-19 that required ventilatory support [21,27-29]. Therefore, the incidence and type of residual interstitial CT abnormalities seems to depend on the severity of the COVID-19 acute phase.

Understanding the post-COVID-19 lung syndrome is complicated due to the varying interpretation of radiological CT findings among the studies, the limited number of longitudinal cohorts analyzing data over time, and the scant information concerning histologic correlation in the different time-points of post-acute COVID-19 lung remodeling. Furthermore, the methodology for analyzing the type and extension of interstitial CT abnormalities is extremely variable depending on the study, especially for identifying interstitial fibrosis [30]. A recent classification of radiological CT post-covid19 interstitial persistent changes has been proposed: 1) predominantly ground glass; 2) mixed ground glass and fibrotic; 3) predominantly fibrotic [30] (Figure 1). This differentiation could help in the clinical practice to better analyze the long-term predictive factors and setting the potential differences in the initial treatment strategies of post-acute persistent interstitial changes [15]. Predominant ground glass opacities are more frequent than fibrotic signs during the initial months after discharge [2,5,10-14,21-30]. Other frequent post-covid CT abnormalities are decreased attenuation areas attributed to small airways disease or hypoperfusion [31]. Identified predictive factors of persistent fibrotic changes at six and twelve months include age and severity of acute phase [13,22,25,27,29].

Table 1 Most frequent persistent symptoms after COVID-19 infection

Organ or system	Persistent post-COVID-19 symptoms
Respiratory system	Dyspnea Anosmia and/or ageusia Cough Difficulties for deep breathing Chest pain
Muscle deconditioning	Muscle weakness Muscle pain
Neurocognitive	Difficulties to pay attention Loss of short-term memory Poor quality of sleep Insomnia Nightmares
Psychological	Anxiety Depression
Digestive	Chocking Feeling of stomach bloating Diarrhea
Cardiovascular	High arterial pressure Tachycardia
Others	Weight lost Autoimmune disorders/signs

Through the inflammatory response, SARS-CoV-2 could activate different mediators of the coagulation cascade as well as cause an endothelial dysfunction after targeting the ACE-2 positive endothelial cells [19,32]. On the chest-CT pulmonary vascular alterations can be seen such as vascular thickening, which is not seen in pneumonia of other etiologies different than covid19 [19]. As we have previously mentioned, decreased DLCO can be observed in many patients which suffered from covid19 pneumonia. However, it is possible that this impairment is not only explained by a restriction mechanism but because of vascular changes [32]. Mejia-Renteria et al performed an observational prospective study in which they showed that patients after the acute phase (>100 days) presented a reduced vascular function compared to control patients as well as compared to patients with acute covid19 pneumonia [33]. Therefore, they suggest that changes in the endothelial cells could lead to vascular dysfunction, contributing to chronic complications of the infection and potential long term-vascular post-covid effects [33].

Although several uncertainties remain to be clarified, prospective ongoing longitudinal studies and multidisciplinary expert consensus will be crucial to better define the post-covid lung patterns and outcomes [17].

POST-COVID LUNG DYSFUNCTION: CLINICAL FOLLOW-UP AND TREATMENT APPROACH

Persistent respiratory symptoms after COVID-19 are investigated by pulmonary follow-up after hospital discharge including forced spirometry, plethysmography, diffusion lung capacity of carbon monoxide (DLCO), and the 6-minutes walking test (6MWT) for measuring exercise capacity and oxygen saturation [9,34-36]. The current statements on post-covid19 recommend a pulmonary follow-up in all hospitalized COVID-19 cases, especially those that required some non-invasive or invasive respiratory supportive therapy during admission [9,34-36]. Most data indicate that the extent of residual abnormal pulmonary parenchymal involvement significantly correlates with DLCO [5,10,12-15,21-29]. Decrease in forced vital capacity (FVC) at 3-months after discharge has been primarily described in those cases that suffered more severe COVID-19 but didn't significantly correlate with the residual CT abnormalities [27]. FVC and DLCO impairment may be due to different post-covid abnormalities, including not only the interstitial changes but also the muscle weakness or endothelial-vascular dysfunction [9]. However, FVC, DLCO and the 6MWT have been useful for monitoring patients with post-covid interstitial syndrome [27]. Radiologically, low-dose CT performed supinely should be sufficient in the majority of post-COVID patients on follow-up [30]. Expiratory CT would be used for those cases with suspicion of distal airflow obstruction [31]. Single or dual energy contrast enhanced (DECT) studies should be performed on those patients with suspicion of vascular involvement, depending on clinical and functional evaluation, for instance those cases with persisting abnormal gas exchange despite normalization of lung parenchyma on CT [30].

Breathlessness and cough are the most common respiratory symptoms in patients with post-covid interstitial or/and vascular persistent abnormalities after severe-critical COVID-19 [5,26-29]. Other frequently associated symptoms are fatigue, neurocognitive dysfunction, psychological and sleep disorders, join pain and muscle weakness [5,13,27-29] (Table 1). Therefore, the initial required therapeutic approach should be multidisciplinary and individualized depending on the patient's needs, but always including functional rehabilitation, symptoms relief and psychological support in a holistic way [9,34-37]. Muscle deconditioning is usually present in COVID-19 survivors, with limited capacity for exercise [37]. Respiratory physiotherapy has demonstrated to be a crucial factor for improving pulmonary function [3,37].

Due to scarcity of published evidence, no agreement exists about the pharmacological treatment of patients after COVID-19 who present with persistent interstitial abnormalities [9,34,35]. However, those symptomatic patients that present respiratory dysfunction and CT predominant ground glass opacities are frequently treated with an empiric systemic steroid treatment [15,34]. Strategies to reduce the severity and progression of post-COVID-19 are unclear. An observational prospective study with no placebo-control arm suggested that low-dose corticosteroid treatment in post-covid patients that presented persistent interstitial changes and symptoms at 6 weeks after discharge was well tolerated and associated a rapid significant improvement [15]. No agreement exists for the treatment approach of post-covid patients that present predominant fibrotic persistent CT abnormalities [34]. Initially, considering the potential pro-fibrotic pathways that COVID-19 could trigger by acting on ACE-2 enzyme and inducing alveolar epithelial cell damage (among other pathways), the potential benefit of anti-fibrotic medications was suggested [8,15]. Currently, clinical trials with antifibrotic drugs, nintedanib (NCT04619680,NCT04541680) and pirfenidone (NCT04607928), including patients with predominant pulmonary fibrotic changes after covid are ongoing. The results of these studies will clarify it the anti-fibrotic approach in these specific cases could be beneficial. Finally, lung transplantation has been a treatment option for patients with progressive pulmonary fibrosis and severe respiratory failure after weeks or months from the onset of infection [38].

CONCLUSIONS

Respiratory consequences after COVID-19 infection are common, especially in those cases that required hospitalization and respiratory support during the acute phase and involves muscle and parenchymal dysfunction. The systematic follow-up of severe COVID-19 patients has enabled to identify different types of post-covid respiratory cases that require a patient-centered integral approach, including rehabilitation, respiratory physiotherapy, emotional and nutritional support, as well as an individual evaluation of parenchymal distortion regarding interstitial changes for the potential need of medication (usually low-dose corticosteroids) and thrombotic vascular events (anticoagulant approach). The frequency of post-covid lung sequela will depend on the severity of the acute infection. Therefore, since the severity of the acute infection is decreasing with the advent of covid-vaccination and the last less-severe covid strains, probably the proportion of patients with post-covid lung consequences will decline in the future. However, patients with post-COVID-19 respiratory dysfunction exist and the optimization of their treatment for reducing the potential chronicity remains a challenge. Increasing research evidence is giving us more and better information about how to better manage these patients. But first, the recognition of this healthcare problem by the healthcare authorities is crucial for working together to mitigate the future consequences and also to support the current post-covid patients.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Special issues in pneumonia 2021

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ABSTRACT

The growing population of older people worldwide represents a great challenge for health systems. The elderly are at increased risk of infectious diseases such as pneumonia, which is associated with increased morbidity and mortality related mainly to age-related physiological changes in the immune system (immunosenescence), the presence of multiple chronic comorbidities, and frailty. In pneumonia, microaspiration is recognized as the main pathogenic mechanism; while macroaspiration which refers to the aspiration of a large amount of oropharyngeal or upper gastrointestinal content passing through the vocal cords and trachea into the lungs is identified as "aspiration pneumonia". Although there are strategies for the prevention and management of patients with pneumonia that have been shown to be effective in older people with pneumonia, more research is needed on aspiration pneumonia, its risk factors and outcomes, especially since there are no specific criteria for its diagnosis and consequently, the studies on aspiration pneumonia include heterogeneous populations.

Keywords: pneumonia, aspiration, elderly

ISN'T ALL PNEUMONIA PATHOGENICALLY ASPIRATION?

The answer to this question is yes. Microaspiration is recognized as the main pathogenic mechanism in pneumonia where particulate material and microorganisms are able to enter upper airways and then reach the lower airways and respiratory tract; while macroaspiration which refers to the aspiration of a large-volume of oropharyngeal or upper gastrointestinal content passing through the trachea and larynx into the lungs describes the term "aspiration pneumonia" [1]. Approximately, between 10% to 30% of hospitalized patients with a diagnosis of community-acquired pneumonia have an illness related to aspiration [2–4]. However, numbers related to aspiration in patients with hospital-acquired pneumonia are scarce. The mortality rate of patients with aspiration pneumonia is higher in comparison to non-aspiration pneumonia. Recently, Gupte et al. [5] reported the burden of mortality from aspiration pneumonia in the United States, with an average of 58,000 deaths per year. The authors also reported 76% of the deaths related to aspiration pneumonia occurred in the group of adults aged ≥75 years old.

The clinical presentation of aspiration pneumonia can be influenced by factors such as bacterial virulence to which the patient is exposed (i.e inoculum size, resistance to antibiotics), risk of recurrent aspiration (more than one episode of pneumonia) and site of acquisition of the aspiration (community, nursing home, hospital) all of which would influence the microbial etiology, therapy and management of the patient [1].

Aspiration events can involve only the airways or the lung parenchyma, or can involve both. The lung infection caused by aspiration can cause unilateral or bilateral infiltrates, usually in gravity-dependent segments of the lung. The basal segments of the lower lobes are affected in individuals in an upright or semi-recumbent position at the time of aspiration (Figure 1A); whereas the posterior segments of the upper lobes are affected in individuals not able to move or change positions in bed (bed bound) (Figure 1B). It is important to known that in central airways, the right bronchus is wider and more straightly aligned with the trachea than the left main bronchus, making this the preferential side for aspirated material to go. Thus, aspiration pneumonia is more common in the right lobes than in the left lobes.

Two clinical consequences can be associated with aspiration; aspiration pneumonia (lung infection caused by a specific

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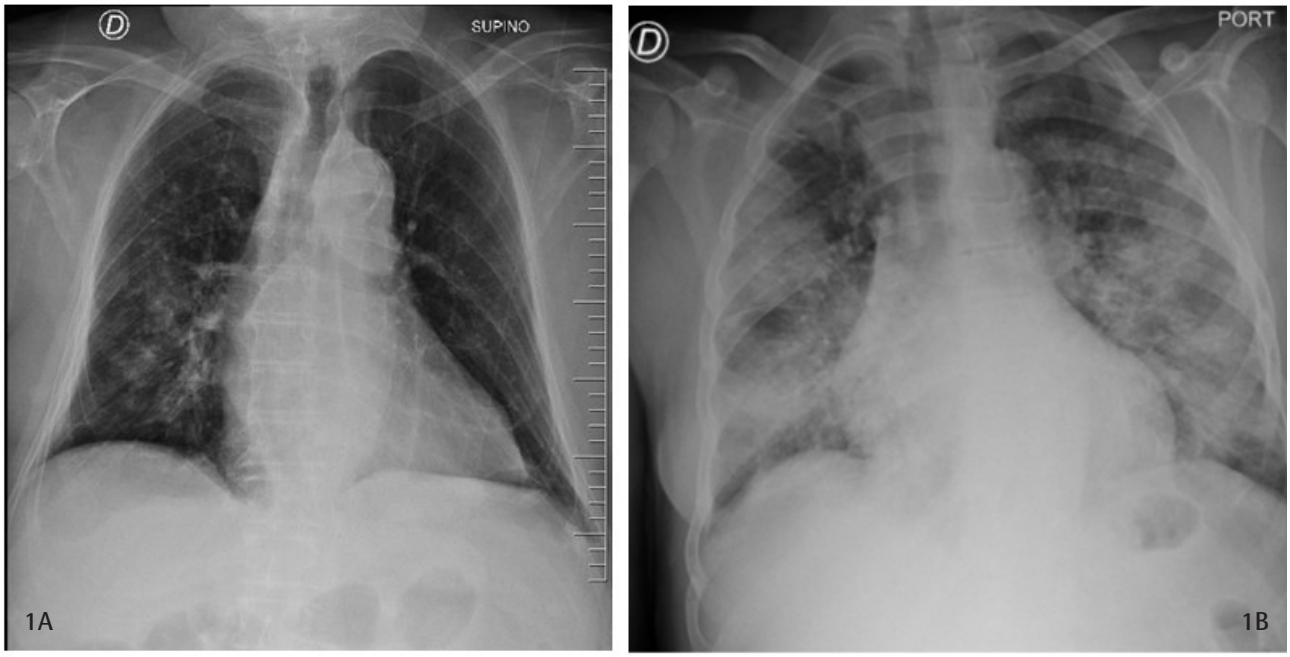

Figure 1 **A) The chest X-ray shows an alveolar inflitrate at right lower lobe, in a 86 year-old patient with moderate cognitive impartiment. The patient live in a nursing-home, present episodes of vomiting and was disoriented.**
B) The chest X-ray shows a bilateral lung infiltrates, respiratory failure, and acute respiratory distress in a 80 year-old patient with repetive episodes of aspiration.

microorganism) and chemical pneumonitis (chemical injury causing inflammation by aspiration of the acid gastric content) [1]. In addition, aspiration of solid material can lead to foreign body aspiration and local endobronchial obstruction.

RISK FACTORS RELATED TO ASPIRATION PNEUMONIA

The factors related to macroaspiration and development of pneumonia include: impaired swallowing (dysphagia, chronic obstructive pulmonary disease, neurological diseases such as stroke or dementia, need of mechanical ventilation), impaired consciousness (acute stroke, head injury, brain lesions, seizures and the effect of some agents that can induce impaired consciousness such as alcohol, drugs, anesthesia or sedatives), increased chance of gastric contents reaching the lung (reflux and tube feeding), and impaired cough reflex (medications, stroke, dementia, impaired consciousness and alcohol). Also, poor dentition in elderly patients could increase the risk of aspiration pneumonia because of the growth of potentially pathogenic anaerobic bacteria.

As we mentioned before, aspiration pneumonia could be multifactorial (Figure 2). Oropharyngeal dysphagia is a relevant risk factor for aspiration pneumonia that is an important area of investigation. In a prospective cohort study of pneumonia patients from Spain [6], of the 134 pneumonia patients analyzed, 55% presented with oropharyngeal dysphagia, and this group of patients was older and often in nursing-homes. Pneumonia was most severe in patients with oropharyngeal dysphagia and has a higher 30-day mortality compared with pneumonia patients without oropharyngeal dysphagia. Similarly, a case- control study [7] that included 36 pneumonia cases and 72 controls (patients with no pneumonia) found that the case group presented with a higher proportion of dysphagia (92% vs 40%, p0.001) than the control group. In this study, oropharyngeal dysphagia was strongly associated with the risk of pneumonia (OR 11.9, 95% CI 3.03–46.9, p0.001).

Another retrospective study [8] that investigated the risk of aspiration pneumonia in patients receiving antipsychotic drugs during hospitalization, reported that of the 146,552 hospitalizations, antipsychotics were used in 10,377 (7.1%) hospitalizations. Aspiration pneumonia occurred in 557 (0.4%) hospitalizations, but the incidence of aspiration pneumonia was 0.3% in unexposed individuals and 1.2% in those with antipsychotic exposure (OR3.9, 95% C = 3.2-4.8). The use of antipsychotics was significantly associated with aspiration pneumonia (aOR1.5, 95% CI = 1.2-1.9).

THE MICROBIOLOGY OF ASPIRATION IS CHANGING

Several studies have demonstrated that the lung microbiome of the individuals with chronic lung diseases differs in diversity and in abundance from lung microbiome of healthy

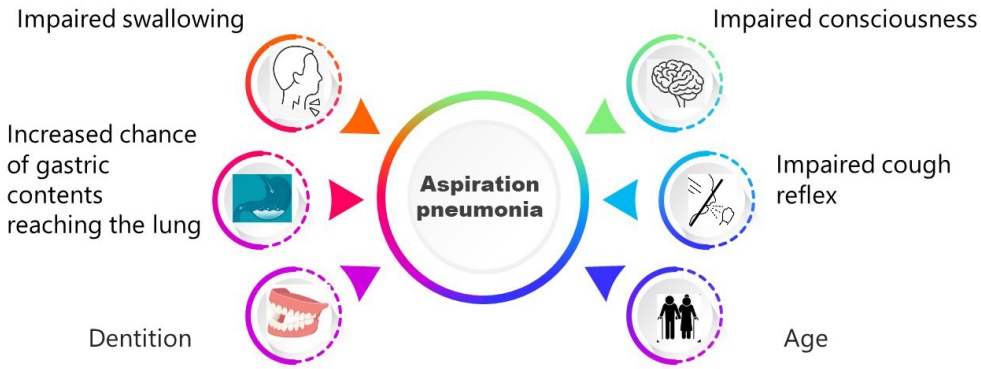

Figure 2 | **Risk Factors for Aspiration Pneumonia**

individuals. We now know that the lung microbiome plays a central role in modulating local inflammation and immune response in lung infections [9]. The lung microbiome shifts in composition during infection or an exacerbation of chronic lung diseases and can become less diverse,which in turn can impair host defenses. Bacteria such as *Prevotella*, *Veillonella*, *Streptococcus*, *Fusobacterium* and *Haemophilus* are common in the normal lung microbiome, and are part of a dynamic community that maintains a constant equilibrium in healthy lungs and these organisms are involved in lung immunity. This equilibrium is disturbed by acute infections, such as pneumonia, or chronic lung diseases. Dysbiosis is the term used to describe this disequilibrium, and is reflected by changes in microbial communities. The risk factors for dysbiosis in aspiration pneumonia and the mechanisms that cause disease are only partly understood [10].

Microbial etiology of aspiration pneumonia has changed over time. Currently, microorganism such as *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* and *Enterobacteriaceae* are the most common organisms. In a recent retrospective multi-institutional joint research from Japan were **1,800 patients with pneumonia were included, the ratio of aspiration pneumonia to total pneumonia** cases increased with age, and 38% of the patients had aspiration pneumonia [11]. There were significant differences between the microbial etiology between patients with aspiration pneumonia and patients without aspiration pneumonia, with a higher frequency of *S. aureus*, *Klebsiella* spp., and *Escherichia coli*, and a lower frequency of *S. pneumoniae*, and *H. influenzae* in the aspiration group. The detection rate of anaerobic bacteria was low in both groups.

Another prospective study that investigated the etiology of hospitalized patients with severe aspiration pneumonia, reported that the three most common microorganism were gram negative bacteria (*E. coli*, *K. pneumoniae, Serratia* spp. and *Proteus* spp.), *S. aureus* and *S. pneumoniae* [12]. Anaerobes were uncommon.

CLINICAL FEATURES OF ASPIRATION PNEUMONIA

An interesting retrospective study from Japan [13] investigated the clinical features and outcomes of patients with aspiration pneumonia in comparison to patients with non-aspiration pneumonia. The study included a total of 214 consecutive patients with pneumonia. Of all the patients, 47% had aspiration pneumonia and 36% had health care associated pneumonia (HCAP). Aspiration was diagnosed in 34% of the CAP patients and in 70% of the HCAP patients. The authors reported three main differences between patients with aspiration pneumonia in comparison to patients without aspiration pneumonia. The first characteristic that the authors found was that patients with aspiration pneumonia had specific host factors and were older, had more frailty, had lower Body Mass Index (BMI) and were more often from nursing home. The second characteristic was related to the severity of pneumonia. Aspiration pneumonia was more severe (severity scores were higher) and more frequently needed intensive care therapy. Finally, the authors observed that patients with aspiration pneumonia had worse outcomes, these patients also presented longer length of stay, had higher rates of pneumonia recurrence and mortality. The most frequent pathogens related to aspiration pneumonia *were S. aureus, S. pneumoniae, Klebsiella* spp. and *E. coli.*

A systematic review and meta-analysis (19 studies) that investigated the outcomes of aspiration pneumonia in CAP patients reported that aspiration pneumonia increased in-hospital mortality (RR, 3.62; 95% CI, 2.65-4.96; $P < 0.001$) and 30-day mortality (3.57; 2.18-5.86; $P < 0.001$). On the other hand, the authors found that aspiration pneumonia was associated with decreased ICU mortality (RR, 0.40; 95% CI, 0.26-0.60; $P < 0.00001$) [14].

Aspiration pneumonia is an acute process that may present with mild symptoms to severe distress associated to respiratory failure. Host factors, chronic comorbidities and functional status are related to presentation and severity of aspiration pneumonia. In elderly patients aspiration pneumonia is often related to poor outcomes.

Figure 3 | **Algorithmic approach to antibiotic therapy for aspiration pneumonia [1].**

CHEMICAL PNEUMONITIS

Chemical pneumonitis is characterized by the macroaspiration of a large volume of gastric contents with a pH<2.5, leading to acute hypoxemia, fever, tachycardia, abnormal chest x-ray and the presence of crackles or wheezes on physical examination. In approximately 16% of the cases of chemical pneumonitis the patients developed acute respiratory distress syndrome (ARDS) [15].

In a study that characterized a cohort of patients who aspirate and require hospitalization, the authors reported that of the 5,584 patients at risk for ARDS and who required hospitalization, aspiration was present in 212 (4%). The authors found that patients who aspirated were with more often male, admitted from a nursing home, had a history of alcohol abuse, and had a lower Glasgow Coma Scale. Aspiration patients were sicker (higher APACHE II score), required more mechanical ventilation, developed more moderate to severe ARDS, and had higher in-hospital mortality rate [16].

RADIOGRAPHIC AND CT DIAGNOSIS

For the diagnosis of aspiration, pneumonia, it is necessary to get confirmation by chest X-ray or computed tomography (CT) scans that are considered the gold standard for the diagnosis of aspiration pneumonia. However, in some cases the chest x-ray may be negative as reported by the study of Miyashita et al. [17] that found negative chest x-ray in 28% of the pneumonia cases that CT scan confirmed. Importantly, in frail patients or in patients who are bedridden, lung ultrasound may be an alternative and complementary approach that can help with the diagnosis of pneumonia. In a patient with suggestive clinical symptoms, presence of pulmonary infiltrates especially in the lower right lobes, the diagnosis of aspiration pneumonia is highly probable [1].

THERAPY OF ASPIRATION PNEUMONIA

For the decision about antimicrobial therapy the determinant factor is the site of aspiration (community, hospital or long term care facility) and risk factors for resistant pathogens. Other determinant factors for antimicrobial therapy are the presence of an abnormal or normal chest x-ray and the severity of the presentation. An algorithmic approach to antibiotic therapy for aspiration pneumonia was proposed by Mandell and Niederman [1]. Figure 3 summarizes this algorithm.

In chemical pneumonitis antibiotics are not recommended. However, in severe cases antibiotics should initiate empirically and the duration of the antibiotics should by guide with the clinical course of the patient.

CONCLUSION

Aspiration pneumonia occurs in characteristic anatomical locations, usually with well-defined risk factors. We should distinguish infectious aspiration pneumonia from chemical aspirations. The microbial etiology of aspiration pneumonia has changed in the last few years, with anaerobes playing a less important role than in the past.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Special issues in pneumonia 2021

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Top-ten papers in pneumonia (2020-2021)

Servicio de Medicina Intensiva. Hospital Universitario y Politécnico La Fe. Valencia, Spain. Study group of infections in critically ill patients (GEIPC-SEIMC).

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ABSTRACT

Despite the fact that the last year has been marked by the SARS-CoV-2 pandemic, there have been many articles published on non-COVID pneumonia. Making the selection has not been easy, having based on those articles that we think can bring us some novelty and help in clinical practice. We have divided the selection into seven sections: patient severity, diagnosis, treatment, ventilation, novelties in the guidelines, fungal infection and organ donation.

Keywords: severe community-acquired pneumonia, nosocomial pneumonia, mechanical ventilation-associated pneumonia

INTRODUCTION

In a year marked by the SARS-CoV-2 pandemic, we thought that publications on non-COVID-19 pneumonia would be scarce, however, after a first review on severe pneumonia, nosocomial pneumonia and ventilator associated pneumonia (VAP), we found more than 3000 articles. We have made the selection based on those articles that we think may provide us with something new and that may help us in our healthcare practice, and, obviously, it does not have to coincide with what any of our readers would have made.

We have structured the selection in 7 parts:

1) Patient severity
2) Diagnosis
3) Treatment
4) Ventilation
5) What´s new in the guides
6) Fungal infection
7) Organ donation

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PATIENT SEVERITY

We begin the review from the arrival of the patient to the emergency room, assessing the severity of the patient and the predictors of mortality, to decide where we admit the patient.

In the first article, Carmo et al. [1] assess whether pneumonia severity scores adequately predict mortality in critically ill patients admitted with pneumonia. To do this, they conduct a three-year prospective observational cohort study (2015-2018) in which they study both the intensive care unit (ICU) severity scores (SAPS 3, qSOFA) and the pneumonia severity scores (CURB-65 and CRB-65). With the variables related to mortality in the multivariate analysis, they elaborate a prognostic score, the pneumonia shock score (PSS) (table 1), so that a PSS ≥ 3 carries a mortality > 26%. They compare this score with SAPS 3, CURB-65, CRB-65 and qSOFA, and observe that it is the one with the best sensitivity, and a higher specificity than pneumonia severity scores. They then use an external validation cohort where they get the same results. The authors conclude that the PSS is a new tool that can help select pa-

Table 1 **Pneumonia Shock Score**

Parameter	Points
Age > 75 years	2
Septic shock	2
Heart rate ≥ 110 bpm	1
Hematocrit ≤ 38%	1
Leukocytes > 15000/mm^3	1
Sodium ≥ 145 mEq/L	1
FiO2 ≥ 30%	1
Obnubilation (GCS < 15)	1

tients who should be admitted to the ICU, and offers an alternative prognostic tool with a great performance in predicting mortality.

In the letter to the editor about this article, Reyes et al [2] study this new score as a long-term predictor, and note that PSS is superior to SAPS-3, CURB-65, CRB-65 and qSOFA in predicting hospital mortality, but that as a long-term predictor its sensitivity and specificity decreases dramatically.

In the following article, Gautam et al [3] consider whether procalcitonin (PCT) should be used as a marker of bacterial co-infection during a viral respiratory infection. They conducted an 18-month retrospective cohort study comparing patients with pure viral respiratory infection with patients with bacterial co-infection observing that the latter have a higher PCT, greater severity, and higher mortality. However, when both cohorts are matched by severity, the specificity of PCT for bacterial coinfection decreases (from 72% to 61%). They then develop a murine model where they infect mice with influenza viruses and see that PCT rises in relation to markers of severity. The authors conclude that PCT is elevated during pure viral infection in proportion to disease severity. Data from the study suggest that PCT is a better indicator of disease severity than bacterial co-infection during viral respiratory infection.

DIAGNOSIS

On the basis that there is no gold standard for the diagnosis of nosocomial pneumonia, the authors of this review [4] review all the tools we have. They begin with imaging techniques, where the low sensitivity and specificity of the chest X-ray stands out, the greater sensitivity of the thoracic computed tomography (CT) and the fact that their findings are not specific, ending the section with lung ultrasound (LUS), which have a greater sensitivity (95%) and a high specificity (91,3%) when they are performed serially.

Within the microbiological techniques we have those based on culture (highlighting the importance of colony counting to distinguish between colonization and infection), and molecular diagnostic techniques, highlighting their speed and their high sensitivity and specificity, differentiating between the different existing platforms.

Finally, the authors comment on some biomarkers remarking that they are not recommended in the nosocomial pneumonia guidelines due to their lack of precision; and name metabolomics and artificial intelligence as the immediate future in diagnosis.

Given the current importance of LUS as a point-of-care, the following article is a study conducted by Haaksma et al. [5] whose objectives were to determine the diagnostic accuracy of dynamic air bronchogram and color Doppler imaging for the diagnosis of pneumonia in patients with consolidation on chest radiograph. This is a prospective diagnostic accuracy study carried out in two periods (September 2018 – January 2020 and September 2020 – December 2020) in which patients with chest X-ray with some consolidations are included, performing a LUS within 24 hours of the X-ray, and another follow-up at 72h., and with the results obtained they elaborate a decision tree. They observe that the air bronchogram has a specificity of 99% and a positive predictive value (PPV) of 96%, with a low sensitivity, on the contrary, the color Doppler has a sensitivity of 90%, with a negative predictive value (NPV) of 90%, while the elaborate decision tree presents a sensitivity and specificity of 86%, and a NPV of 90%. When comparing their results with the BLUE protocol, and with the sCPIS and lusCPIS scores, they conclude that in ICU patients with pulmonary consolidation on chest X-ray, an extended lung ultrasound protocol based on the evaluation of air bronchograms and measurements of pulsatile flow is an accurate and directly bedside available tool to differentiate pneumonia and atelectasis. It outperforms standard lung ultrasound and clinical scores.

TREATAMENT

Within the section of treatment, the first work selected is that of Mahmood and Shorr [6] in which they review the pharmacokinetics and pharmacodynamics of antibiotics. Within the pharmacokinetics, the importance of the penetration of the drug into the lung in the case of pneumonia stands out, a fact that we lack in most antibiotics of routine use. Regarding pharmacodynamics, they emphasize the increased renal clearance, defined as GRF > 130 ml/min/ 1.73 m^2, which appears in more than 30% of critical patients, and in which the estimation of glomerular filtration rate may be underestimated. In patients with increased renal clearance, antibiotics with renal metabolism are eliminated more quickly, so we are underdosing antibiotics (especially β-lactams, carbapenems and vancomycin).

We are not yet clear whether we should use corticosteroids in the treatment of pneumonia. To try to shed some light on the subject we have chosen the article by Póvoa et al [7] whose objective is to evaluate the evidence and recommendations of the prescription of corticosteroids as an adjuvant treatment in severe community acquired pneumonia (CAP). They conclude that only in moderate-severe *Pneumocistys jiroveci* pneumonia in HIV patients have corticosteroids been shown to decrease mortality, and in varicella pneumonia they have a positive influence on prognosis. In the case of other pathogens, corticosteroids have been shown to increase mortality (influenza pneumonia), or a clear effect on prognosis has not been defined. With the available evidence its use in severe CAP is not recommended in the latest published guidelines. In addition, it is necessary to improve the characterization of corticosteroids in terms of type and efficacy, dose, route of administration, duration of treatment, and possible interactions with other treatments administered such as macrolides.

VENTILATION

In recent years, there has been a great development of both non-invasive ventilation and the use of high flow, in ICUs

and in hospitalization wards. Cutuli et al. [8] reviews these two types of oxygen therapy in CAP. In this work they make an interesting review about the pathophysiology of acute respiratory failure (hypoxemic and hypercapnic) indicating that they can provide us in each of them with these types of ventilation and when we should use each of them. Highlight the importance of early identification of treatment failure with non-invasive respiratory support, to prevent delayed orotracheal intubation and protective invasive mechanical ventilation.

WHAT'S NEW IN THE GUIDES

Although in the last year most management and treatment publications and guidelines have focused on SARS-CoV-2, some guidelines on CAP and nosocomial pneumonia have been published. In this paper, Martin-Loeches and Torres [9] highlight recent advances in guidelines for the treatment of severe CAP. Regarding the etiology, they emphasize the importance of their knowledge through molecular techniques with the main objective of adjusting antibiotic treatment in order to reduce treatment failure and overuse of antimicrobials. They emphasize the importance of prognostic scores to decide the location of the patient, so that the best score to decide hospital admission is the PSI, while for admission to the ICU the major and lower criteria of the IDSA/ATS should be used. Regarding the duration of antibiotic treatment, a balance should be made between clinical success and the need to avoid the development of antibiotic resistance. Finally, biomarkers should be a mainstay in the management of patients with CAP, especially in severe forms, to decrease treatment failure.

FUNGAL INFECTION

Within a review on severe pneumonia, we cannot forget about fungal pneumonias. In this section we highlight the work carried out by Loughlin et al. [10], whose objective was to estimate the prevalence of Aspergillus infection in ventilated patients, not neutropenic, with suspected pneumonia associated with mechanical ventilation. To this end, they carried out 2 multicenter prospective studies between February 2012 and September 2016, in patients from whom they obtained serum and BAL mycological samples, diagnosing them with probable aspergillosis according to clinical, radiological and mycological criteria. Of a total of 194 patients, they identified 12.4% who met criteria for probable aspergillosis, with higher mortality in the ICU than those who did not meet the diagnostic criteria, and with a longer stay in the ICU. As discussed in the editorial [11], aspergillus is a more frequent cause of VAP in non-immunosuppressed patients than we think, and by applying non-culture-based diagnostic methods such as galactomannan in BAL and serum, some additional cases can be diagnosed.

ORGAN DONATION

Initially, choosing one last article among the many that have been published this last year on other topics such as pneumonia in immunocompromised, prevention, microbiota, omics, artificial intelligence, etc. was not easy, until we found the next work because of the importance we consider it may have. The work of Poignant et al. [12] is the only one we have found on pneumonia and organ donation. This is a 4-year multicenter observational retrospective cohort study (January 2013 - December 2016) whose objectives were to describe the clinical and microbiological characteristics of bacterial pneumonia in brain-dead patients and to assess the impact of pneumonia on lung suitability for extraction in patients without initial contraindication to donation. The results show that among the patients proposed for lung donation, 27,4% presented aspiration pneumonia, and 8,2% had early VAP. In the multivariate analysis, the independent predictors of pneumonia in brain-dead patients were age, anoxic brain damage, aspiration before or during tracheal intubation, and no antimicrobial use at day 1. Among the authors' conclusions, it stands out that the initiation of antibiotic prophylaxis on the first day of stay in the ICU in comatose patients with severe brain damage could increase the current pool of lung donors.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Special issues in pneumonia 2021

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Diagnostic and therapeutic approach to occupational pneumonia

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ABSTRACT

We shall define occupational pneumonia as a disease of external origin, closely tied to the workplace setting and caused by biological microorganisms. The main pathogens are bacteria, fungi and viruses. There are a number of occupations specifically prone to the possibility of acquiring pneumonia when performing work duties.

In addition to the diagnostic methods and drug treatments current in infectious processes, a good clinical history, with avoidance and protection measures would be the most important tools for the management of occupational pneumonia.

Social and demographic changes in the last two decades have made zoonotic infections, and especially viruses, the main cause of new infections. Human health and animal health are closely linked, so collaboration between veterinarians and doctors, together with the necessary environmental respect and conservation, plus the appropriate public policies are essential to avoid these wide negative effects.

Keywords: Ocupaccional infections, comunity pneumonia, zoonotic infections, early diagnostic tests

INTRODUCTION

We shall define work-related or occupational pneumonia as a disease of external origin, which is closely tied to the workplace setting and caused by biological pathogens, including genetically modified pathogens and cell cultures, thereby leaving out the contracting of the disease in the community outside the workplace. With this definition, we therefore exclude from this review cases of occupational pneumonia caused by inorganic substances or allergic pneumonitis.

Community-acquired pneumonia (CAP) is not considered a work-related or occupational disease, so it is difficult to know how prone to develop it different occupations and working conditions may make workers. It is difficult to attribute pneumonia to an occupational or work-related source,when exposure to the pathogen is also present in the community. However, there are occupations that necessarily involve contact with certain pathogens to a higher or lesser degree, and thus give rise to the possibility of acquiring pneumonia while performing one's duties. These are listed as such in the Royal Decree on Occupational Diseases that we will be discussing later.

Improvements in hygiene and prevention have meant that some of these pneumonias, especially those of bacterial origin, have shown a marked decrease throughout the 20th century, to the point where they are now anecdotal. On the other hand, zoonotic infections, especially those due to emerging viruses, such as avian influenza (bird flu) or the coronavirus, are increasingly causing severe pneumonia after overt occupational exposure [1].

In this chapter we will be discussing some of the determining factors for the ways these pathogens spread, the occupations associated with pneumonia and the pathogens that cause it, as well as diagnostic and therapeutic approaches, followed by some final reflections on the future of these infections.

DISEASE SPREAD IN THE WORKPLACE AND ITS DETERMINING FACTORS

In the workplace, pneumonia-causing pathogens are usually transmitted mainly by the inhalation of infectious particles present in the environment, and only more rarely following

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bacteremia. As for the initial host, up to 75% of cases are of animal orign directly (zoonosis) or from the manipulation of animal-derived products, while on other occasions transmission originates in other human beings, as is the case of the flu or the coronavirus, as clearly shown in the health care setting [2].

The determining factors, as in other types of pneumonia, will depend both on the toxic effect of the inhaled pathogen and the intensity and duration of exposure, as well as how susceptible the infected host is.

It should also be noted that certain working conditions, involving contact with dust and sudden changes in temperature, behave as added risk factors rather than as causes of pneumonia [3].

OCCUPATIONS RELATED TO PNEUMONIA CASES ACQUIRED IN THE WORKPLACE

There are a number of occupations or risky activities related to the risk of acquiring pneumonia while performing work duties. These are listed as such in section 3 of Royal Decree RD 1299/2006, which provides a table of those occupational diseases approved by the Social Security system and establishes criteria for their notification and registration in Spain (Table1 [4]).

As a summary, we highlight the following occupations:

- Health care and laboratory personnel
- Veterinarians and staff who are in contact with animals
- Workers who work with and handle waste and human or animal excreta
- Farmworkers, nature conservation and exploration workers, hunters
- Construction workers and law enforcement agents

MAIN PATHOGENS CAUSING OCCUPATIONAL PNEUMONIA

Among the main disease-causing pathogens of occupational pneumonia, we include bacteria, fungi and viruses, as reflected in Table 2.

Bacteria: *Francisella tularensis, Leptospira interrogans, Burkholderia pseudomallei, Bacillus anthracis*, and some other more frequent bacteria such as *Coxiella burnetii, Chlamydophila psittacii, Legionella pneumophila, Mycoplasma pneumoniae*

Fungi: *Aspergillus*, *Histoplasma capsulatum, Coccidiodes immitis, Blastomyces*

Virus: Hantavirus, *Influenzae* (bird flu, swine flu) coronavirus (SARS, MERS, SARS-CoV-2)

In this brief review, we discuss some of these pathogens and the characteristics of each infection. There are pneumonic diseases caused by bacteria closely related to certain occupations, which were prominent in the past but are currently diagnosed only sporadically, such as tularemia, leptospirosis, anthrax or melioidosis. On the other hand, other diseases such as Q Fever, psittacosis or legionellosis are more common today and can be acquired both in the workplace and in the community.

Table 1 Professions related to occupational pneumonic processes

CODE	PROFESSIONS
3B0101	Farmers
3B0102	Ranchers
3B0103	Butchers
3B0104	Furriers
3B0105	Tanners
3B0106	Veterinarians
3B0107	Leather garment designers
3B0108	Handling, loading, unloading, transport and use of animal offal
3B0109	Shepherds
3B0110	Health personnel
3B0111	Laboratory personnel
3B0112	Slaughterhouse staff
3B0113	Personnel that care, collect, breed and transport animals
3B0114	Rural workers
3B0115	Butchers
3B0116	Veterinarians
3B0117	Poultry farmers
3B0118	Pet shops
3B0119	Work with risks of injury in a potentially dangerous environment
3B0120	Handling of human or animal excreta
3B0121	Farmers
3B0122	Game warden
3B0123	Forestry work
3B0124	Farm workers
3B0125	Paddy field reapers
3B0126	Swineherds
3B0127	Sewer works (rats)
3B0128	Cowboys
3B0129	Professions in contact with equine livestock
3B0130	Nature Conservation personnel
3B0131	Law enforcement personnel
3B0132	Jobs involving handling or exposure of animal excreta: ranchers

*Occupational diseases approved by Social Security System in Spain [4].

Table 2 Microorganisms associated with occupational pneumonia.

Disease (pathogen)	Reservoir	Risk populations
Bacteria		
Respiratory tularemia (*Francisella tularensis*)	Wild rabbits and rodents	Laborers, Military Personnel, Laboratory Workers, Hunters/Trappers, Agricultural Workers
Leptospirosis (*Leptospira interrogans*)	Water, soil, rodent urine	Farmers and veterinarians
Melioidosis (*Burkholderia pseudomallei*)	Soil, stagnant water, rice fields	Military personnel, agricultural workers
Inhalation anthrax (*Bacillus anthracis*)	Animal products (wool, fur)	Agricultural workers, tanners, slaughterhouse workers, textile workers, laboratory workers
Ornithosis (*Chlamydophyla psittaci*)	Birds	Pet shop workers, poultry production workers, veterinary care workers, laboratory workers
Q Fever (*Coxiella burnetii*)	Domesticated animals (cattle, sheep, goats)	Laboratory workers, textile workers, slaughterhouse workers, dairy cattle workers, veterinary care workers
Legionnaire's disease (*Legionella* spp.)	Contaminated water sources (for example, cooling towers, evaporative condensers)	Healthcare workers, laboratory workers, industrial laboratory workers, water well diggers
Atypical pneumonia (*Mycoplasma pneumoniae*)	Humans	Military personnel, healthcare workers, institutional workers
Fungi/Mycobacteria		
Histoplasmosis (*Histoplasma capsulatum*)	Earth; bird or bat droppings (endemic to eastern North America)	Agricultural workers, laboratory workers, manual workers
Coccidioidomycosis (*Coccidioides immitis*)	Soil (endemic to western North America)	Military personnel, agricultural workers, manual workers, textile workers, laboratory workers
Blastomycosis (*Blastomyces dermatitidis*)	Soil (endemic to eastern North America)	Laboratory workers, agricultural workers, manual workers, forestry workers
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Soil (endemic to Venezuela, Colombia, Brazil)	Farm workers
Sporotrichosis (*Sporothrix schenkii*)	Plant debris, tree bark and garden plants	Gardeners, florists, miners
Tuberculosis (*Mycobacterium tuberculosis, M. bovis, M. africanum*)	Humans and cattle	Laboratory and health care workers, slaughterhouse workers, veterinary care workers
Virus		
Hantavirus	Rodents	Farm workers, herders, rodent control workers
Measles	Humans	Healthcare and laboratory workers
Rubella	Humans	Healthcare and laboratory workers
Varicella zoster	Humans	Healthcare and laboratory workers, military personnel
Respiratory syncytial virus	Humans	Healthcare and laboratory workers
Adenovirus	Humans	Healthcare and laboratory workers, military personnel
Parainfluenza virus	Humans	Healthcare and laboratory workers
Influenza	Humans	Healthcare and laboratory workers
Coronavirus	Humans	Healthcare and laboratory workers

BACTERIA

Tularemia [5]. This is a disease caused by *F. tularensis*, an obligate intracellular Gram-coccobacillus. The reservoir is usually rodents (hares, rabbits...) and it can be acquired by inhalation, which causes pneumonia, or by insect bites, which produces an ulceroglandular form that is the most frequent. It is not transmitted between people. When it affects the lung, it causes lobar infiltrates, lymphadenopathy and, on occasion, effusion. Diagnosis is through blood tests, by culture (rich in cysteine), which gives a late result, and by PCR tests. Treatment is with antibiotics (aminoglycosides, doxycycline, or fluoroquinolones).

Leptospirosis [6]. Disease caused by L. *interrogans*. The reservoir is found in rodents (rats), as well as in water and soil contaminated with rodent urine. It commonly presents as pneumonia with bilateral infiltrates (pulmonary hemorrhage), but it can also present with jaundice and renal failure, then completing a Weil's syndrome triad. Diagnosis is through serological methods, by sample culture and recently also by PCR. Treatment is with penicillin or tetracycline and there is also a vaccine for cattle (which can occasionally act as reservoir).

Anthrax [7,8]. A rare disease caused by *B. anthracis*, a Gram-positive bacillus, whose reservoir consists of herbivorous animals (lambs, goats, cows) and is transmitted through skin contact with animals (carbuncle) or through inhalation of spores, which causes a pneumonia condition characterized by bilateral alveolar infiltrates or even necrotizing pneumonia, which may present mediastinal widening due to mediastinitis. In 2001 there was a case of bioterrorism in the US, following the mailing of several envelopes containing bacillus spores. Diagnosis is based on blood tests and through sample cultures. Treatment requires high doses of antibiotics, initially in combination with penicillin/tetracyclines and fluoroquinolones. Since this bacillus produces toxins, there is an antitoxin treatment. There is also a vaccine for cattle.

Melioidosis [9]. Disease caused by the Gram-negative bacteria, *B. pseudomallei*. It is found in soil and water in endemic areas in Southeast Asia, as well as in India and China. After pathogen inhalation, pneumonia can present with infiltrates or cavitated lesions. Symptoms can take up months to appear, so the epidemiological study is very important. In the 1960s, several cases were diagnosed after the return home of American soldiers from the Vietnam War. Diagnosis is made by staining and culture. Serological diagnosis is unreliable in endemic areas. Treatment is long-term, with ceftazidime, imipenem, or piperacillin. It is usually resistant to colistin and aminoglycosides.

Q fever [10]. Disease caused by *C. burnetii,* whose reservoir consists of domestic and wild animals, and ornithosis or psittacosis [11] caused by *C. psittaci*, whose reservoir is birds, can both manifest as pneumonia after inhalation of *Coxiella* spores or dust contaminated with bird droppings. The clinical and X-ray picture is usually similar to that found in community pneumonia. The usual diagnostic methods are serological tests, since sample culture is complicated and risky for laboratory personnel. New diagnostic molecular techniques, such as PCR, are being more widely used. The treatment is with macrolides or quinolones.

FUNGI

Histoplasmosis [12]. Disease caused by *H. capsulatum*. It is usually found in soils contaminated with bird and bat droppings, with a high nitrogen content. Often found in endemic areas of Central and South America, Africa, Asia and Australia. Its transmission is by inhalation of conidia, which occurs after turning over large amounts of soil, but a large amount of inoculum is needed to cause pneumonia. 90% of cases are asymptomatic, so calcified pulmonary nodules can be seen as an incidental finding on a chest X-ray, but when the inoculum is sizable, pneumonia symptoms can take shape, presenting pulmonary infiltrates with hilar lymphadenopathies and mediastinal widening. Diagnosis is made by tissue staining, slow-growing culture, serological tests and antigen detection. Treatment is unnecessary in many cases and only in severe forms, azoles or amphotericin B are prescribed.

Coccidiomycosis [13]. Disease caused by *C. immitis,* a fungus that lives on soil, which is more common in dry summers and in endemic desert areas such as Arizona, California or New Mexico. Transmission occurs through inhalation of spores following soil disturbance. Two-thirds of affected patients have few or no symptoms. When the spores affect the lung, they usually manifest radiologically as infiltrates, often involving cavitary lesions and lymphadenopathies. Sometimes these infiltrates do not resolve and X-ray images show persistent solitary nodules in the lung periphery. Diagnosis is through serology, histological (after digestion with potassium hydroxide, or papanicolaou) and by culture. Treatment is not necessary in many cases, and when necessary, azoles or amphotericin B are used.

VIRUSES

Hantavirus [14]. There are several types of this virus, whose reservoir is found in different types of rodents that act as vectors and its transmission occurs after inhalation of aerosols derived from the urine, feces or saliva of the vector. It is endemic in the US and South America. When it affects the lung, it causes severe bilateral pneumonia (infiltrated interstitial alveoli), often involving hypotension and shock (cardiopulmonary syndrome). Diagnosis is made through serology and PCR techniques. There is no effective antiviral treatment (ribavirin has shown activity in vitro), so mainly supportive measures are used. There is no vaccine.

Viruses that occasionally circulate in the community, such as measles, rubella, chicken pox or syncytial, can also affect health care professionals and cause pneumonia. Among those causing the most impact in recent years and which can be transmitted between humans are the Influenza virus and the coronavirus [1].

Influenza viruses. There are four types of Influenza viruses (A, B, C, D), with A and B being the types that cause seasonal epidemics, and Influenza A viruses the only type known to cause pandemics. These influenza A viruses are classified based on surface proteins hemagglutinin (H) and neuraminidase (N). There are 18 hemagglutinin and 11 neuraminidase subtypes. In Figure 1, you can see the successive flu pathogens that have affected the human population. The H5 lineage of the Influenza virus is the one causing the most concern in recent years, given that it affects millions of birds and has the potential to be transmitted to humans (figure 1)

Coronavirus. There are 7 types of coronaviruses that infect humans (see figure 2). The first four are very common and

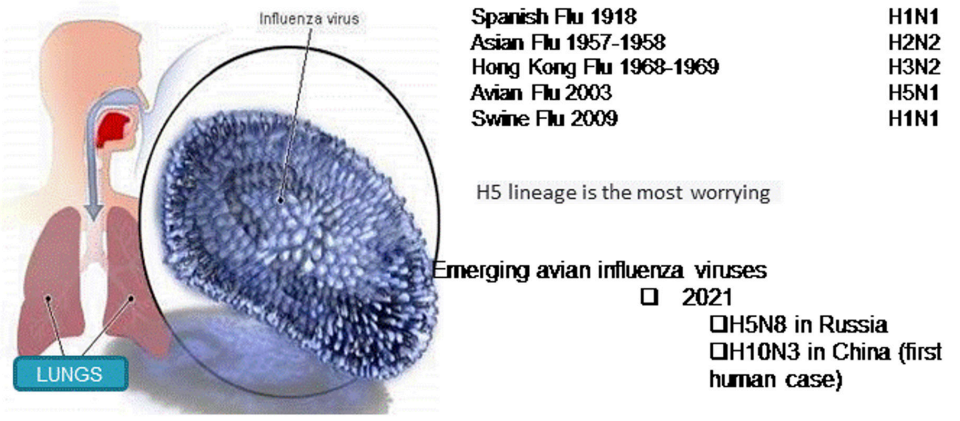
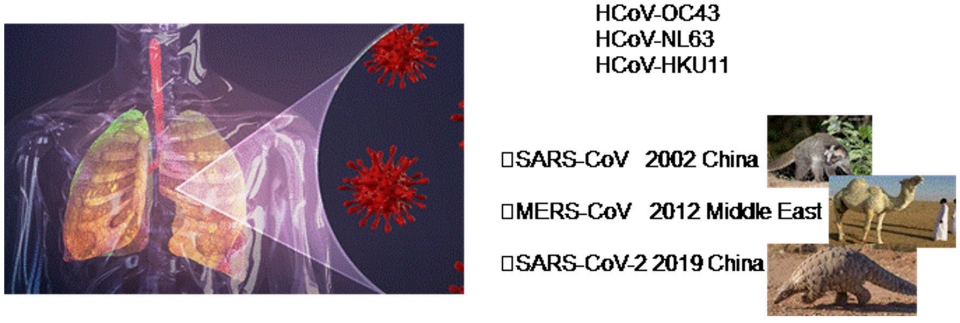


Figure 1 Influenza viruses that affect humans



* HCoV: Human Coronavirus .HCoV-229, HCoV-OC43, HCoV-NL63, HCoV-HKU11, Common coronaviruses that infect humans

*SARS-CoV: Severe Acute Respiratory Sindrome Coronavirus; MERS-CoV : Middle East respiratory Syndrome Coronavirus; SARS- CoV2; Severe Acute Respiratory Sindrome related coronavirus type 2; types of coronavirus that have appeared more recently

Figure 2 Coronaviruses that affect humans.

* HCoV: Human Coronavirus .HCoV-229, HCoV-OC43, HCoV-NL63, HCoV-HKU11, Common coronaviruses that infect humans
*SARS-CoV: Severe Acute Respiratory Sindrome Coronavirus; MERS-CoV : Middle East respiratory Syndrome Coronavirus; SARS-CoV2; Severe Acute Respiratory Sindrome related coronavirus type 2; types of coronavirus that have appeared more recently

often cause colds. However, the other three (SARS-CoV, MERS-CoV and SARS-CoV-2) can cause pneumonia and significant mortality rates, especially the first two, while SARS-CoV-2 has also shown a great ease of transmission.

The huge socio-sanitary repercussions that COVID-19, caused by SARS-CoV-2, has had worldwide, has once again raised our interest in a better understanding and control of emerging zoonotic infections. The risks of zoonoses are accentuated with globalization, wich has enabled its rapid expansion throughout the world. The "posthoc" analysis of recent epidemics such as bird flu or COVD-19, showed that the viruses were already circulating in the population weeks before the first case was diagnosed. This shows our need for earlier detection of future emerging zoonoses [15,16].

THERAPEUTIC DIAGNOSTIC APPROACH

A good clinical history is always very important in medicine, but in work-related or occupational diseases it is the key to indicating a possible diagnosis and being able to order the relevant diagnostic tests.

The diagnostic methods used are the same as those used for community pneumonia, among them:

- Cultures, which can be more or less complex and sometimes slow-growing, making it possible to study sensitivity to antimicrobials
- Histopathological staining techniques, especially when fungi are suspected
- Serology methods (IFI, ELISA)
- Rapid antigen tests
- Nucleic acid amplification tests (PCR), which have revolutionized the diagnosis of infectious diseases

As for therapeutic approaches, like in all work-related diseases, the most important measures are avoidance and protection. Vaccines play a major role in preventing the disease. Once the infection is established, we have at our disposal, as in other types of pneumonia, drug treatments with antibiotics, antifungals and antivirals. As adjuvant therapy, we must consider immunomodulatory drug treatment, which was tried during the recent COVD-19 pandemic. In cases when we do not have very effective therapeutic measures, we will need to resort to life support measures.

CONCLUSIONS

Some of the occupational origin bacterial and fungal pneumonias that were prevalent historically have been decreasing in recent years, due to improvements in prevention. However, social and demographic changes in the last two decades have meant that zoonotic infections, and especially viruses, have become the main cause of new infections or at least had a large increase in incidence.

Human health and that of animals are closely linked, so collaboration between veterinarians and doctors, together with the necessary environmental respect and conservation, plus the appropriate public policies are essential to avoid the negative effects that the development of these zoonoses and communicable diseases can give rise to. To this effect there is a WHO-supported initiative called "One Health" [17,18], which establishes a global collaborative approach to understand the interrelated challenges that human and animal health will face in this promising future.

Among the measures aimed at preventing and/or controlling epidemics/pandemics, we should consider the implementation of strategies based on "early warning" and "rapid response" mechanisms, as well as the development of rapid diagnostic technologies. One of the most important tools we currently have in the diagnostic study of these zoonoses and other infections, is the use of molecular biology techniques applied to the understanding of epidemiology. For an optimal response we should have human resources available, but also specialized laboratories with good communication networks between them and with health care facilities. On the other hand, the use of new technologies such as *big data* and *artificial intelligence* [19] can help us monitor these infections, create predictive algorithms, and discover or develop new treatments.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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Special issues in pneumonia 2021

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Etiology, diagnosis, and management of pneumonia in immunosuppressed patients

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ABSTRACT

Patients with a compromised immune system suffer a wide variety of insults. Pulmonary complications remain a major cause of both morbidity and mortality in immunocompromised patients. When such individuals present with radiographic infiltrates, the clinician faces a diagnostic challenge. The differential diagnosis in this setting is broad and includes both infectious and non-infectious conditions. Evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating, and time-consuming. This common and serious problem results in significant morbidity and mortality, approaching 90%. Infections are the most common causes of both acute and chronic lung diseases leading to respiratory failure. Non-invasive diagnostic methods for evaluation are often of little value, and an invasive procedure (such as bronchoalveolar lavage, transbronchial biopsy or even open lung biopsy) is therefore performed to obtain a microbiologic and histologic diagnosis. Bronchoscopy allows certain identification of some aetiologies, and often allows the exclusion of infectious agents. Early use of computed tomography scanning is able to demonstrate lesions missed by conventional chest X-ray. However, even when a specific diagnosis is made, it might not impact patient's overall survival and outcomes.

Keywords: Immunosuppressed host; opportunistic infections; pneumonia; acute respiratory failure.

INTRODUCTION

Patients with a compromised immune system suffer a wide range of lung diseases. In this subpopulation, pulmonary complications remain a major cause of both morbidity and mortality. When an immunocompromised host presents with radiographic infiltrates, the clinician faces a broad differential diagnosis which includes infectious and non-infectious processes. Furthermore, the radiographic findings can be, in many cases, nonspecific and some of the most common aetiologies may have overlapping clinical and imaging features.

Over the last two decades, scientific evidence has brought to the table different important questions. Firstly, an aggressive diagnostic approach to identify the underlying cause of the disease is necessary, as diagnostic delay increases the risk of mortality. Secondly, the evaluation of these infiltrates usually requires a bronchoscopy. This technique allows an adequate and certain identification of many aetiologies, and usually aids in excluding infectious agents even if the procedure is otherwise unrevealing. Thirdly, the early use of computed tomography (CT) scanning commonly demonstrates lesions that are missed by simple chest radiography. Despite these improvements in the diagnostic tools, initial therapeutic interventions include the use of broad-spectrum antibiotics and other anti-infectives (antiviral and antifungal treatments) in order to ensure that patients are receiving the appropriate therapy [1]. With the microbiological results of these invasive techniques, the treatments are then adjusted. Frustratingly, the outcomes in immunocompromised patients with radiographic lung infiltrates are still poor. Many original and review articles have focused on the management of this condition. The present review attempts to provide a comprehensive and systematic picture of the current knowledge and an integrated approach to these challenging patients.

DIFFERENTIAL DIAGNOSIS

Immunocompromised patients show a wide variety of lung insults. Infections are the most common cause of both acute and chronic lung diseases in these patients, but many other non-infectious conditions affecting the lungs must be considered. The clinical presentation of these non-infectious conditions often

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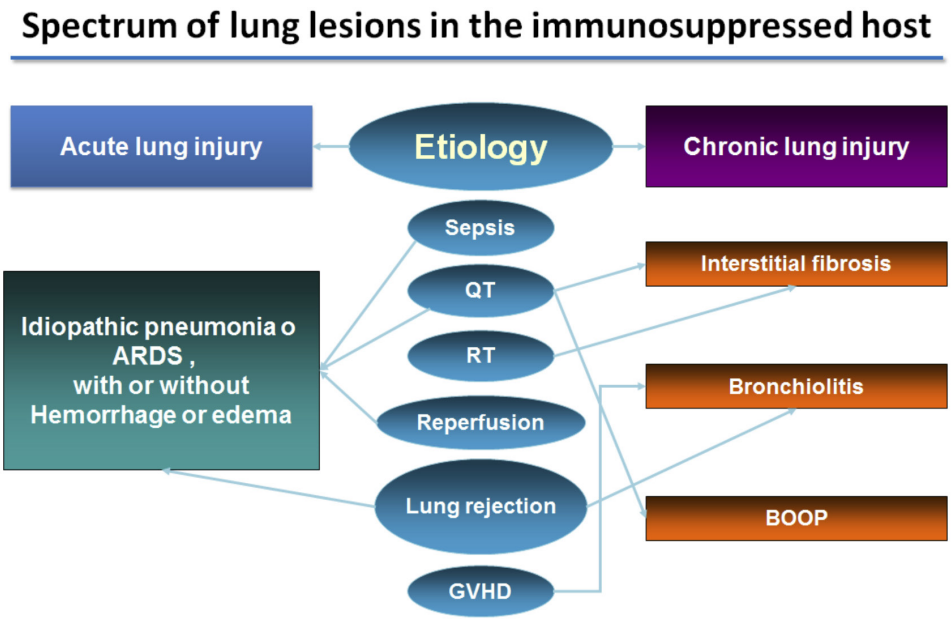

Figure 1 | **Spectrum of lung lesions in the immunosuppressed host**

ARDS: Adult Respiratory Distress Syndrome; BOOP: bronchiolitis obliterans with organizing pneumonia; GVHD: Graft versus host disease; QT: Chemotherapy; RT: Radiotherapy; . Modified and adapted from reference 2

mimics an infectious presentation, thus causing diagnostic dilemmas. The spectrum of non-infectious lung injuries in the immunosuppressed host includes interstitial oedema, interstitial fibrosis, diffuse idiopathic pneumonia, acute respiratory distress syndrome, and obliterative bronchiolitis [2]. Occasionally, alveolar haemorrhage may be present as a secondary complication. Other conditions such as sepsis, irradiation, graft rejection, reperfusion injury, graft-versus-host disease (GVHD), and chemotherapeutic agents and other drug reactions such as biological treatments are also included in the differential diagnosis (Figure 1). These conditions most often present as diffuse pulmonary infiltrates on chest radiograph. Thus, establishing a specific diagnosis and determining the specific aetiology is usually problematic. From a pragmatic standpoint, excluding infectious causes is the principal aim of the diagnostic work algorithm. The expansion of modern microbiological diagnostic techniques based on the detection of genetic products of microorganisms, or their proteins and metabolites, has managed to improve the diagnostic accuracy when facing immunosuppressed patients with pulmonary infiltrates.

The evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating, and time-consuming. This common but serious problem results in significant morbidity and mortality, approaching 90% of patients between both. It is estimated that the lungs are involved in at least 75% of immunocompromised patients with any complication. At autopsy, over 90% of these patients present histological pulmonary affectation. However, in 15% of cases even the pathologist cannot make a definitive diagnosis, which result in non-specific diagnoses such as "diffuse alveolar damage", or "interstitial pneumonitis and fibrosis". Several series of transbronchial lung biopsies, bronchoalveolar lavage (BAL), and even open lung biopsies resulted in similar failure rates (15-30%) in reaching a definitive diagnosis. Yet even when a specific diagnosis is made, it may not necessarily improve the outcome and survival. The mortality rate varies between 15 and 90%, depending on the underlying disease, the severity of lung involvement, and the degree of impairment of the host immunity.

Interstitial and alveolar parenchymal lung changes are two of the most common and serious complications in this group of patients. The morbidity rate reaches 50% and up to 90% if endotracheal intubation and mechanical ventilation are necessary. Opportunistic and bacterial infections are common causes of pulmonary infiltrates, and must be distinguished from other conditions such as drug reactions, volume overload, pulmonary haemorrhage, and malignant diseases. An accurate and prompt diagnosis of potentially treatable causes can be lifesaving. Non-invasive diagnostic methods for evaluation are often of poor value, and invasive procedures (such as BAL, transbronchial biopsy or even open lung biopsy) are therefore performed to obtain a histological diagnosis [3]. Nevertheless, narrowing the diagnostic alternatives should minimize the need for risky, costly, and possibly unnecessary diagnostic and therapeutic interventions. The differential diagnosis of pulmonary infiltrates in the immunocompromised host is summarized and shown in Table 1.

Table 1 Differential diagnosis of pulmonary infiltrates in the immunocompromised host

INFECTIOUS	NON-INFECTIOUS
Viral	Alveolar haemorrhage
CMV, RSV, Influenza, PIV, ADV, SARS-COV-2, HSV, VZV, HHV6	ARDS
Fungal	Acute GVHD
Molds (*Aspergillus*, breakthrough IFI such as *Fusarium, Mucor, Scedosporium, Lomentospora*)	Heart failure
Yeasts (*Pneumocystis jirovecii, Cryptococcus* and emerging yeasts)	Pulmonary / fat embolism
Dimorphic fungi (endemic mycoses)	Hyperleukocyte syndromes
Bacterial	Lymphoma
GNB, GPB, *Nocardia*, mycobacteria	Aspiration
Protozoa and parasites	BOOP
T*oxoplasma, Strongyloides, Paragonimus*, geohelminths	Idiopathic pneumonia or chemotherapy drug toxicity
	Other causes

ADV: adenovirus; ARDS: Adult Respiratory Distress Syndrome; BOOP: bronchiolitis obliterans with organizing pneumonia; CMV: cytomegalovirus; GNB: gram-negative bacteria; GPB: gram-positive bacteria; GVHD: Graft versus host disease; HHV6: human herpes virus-6; HSV: herpes simplex virus; IFI: invasive fungal infection; PIV: parainfluenza virus; RSV: respiratory syncytial virus; VZV: varicella-zoster virus.

OPPORTUNISTIC LUNG INFECTIONS

Opportunistic infections are a major cause of morbidity and mortality in severely immunocompromised patients, such as those under chemotherapy or biological therapies, those with haematological malignancy, aplastic anaemia or advanced and untreated HIV infection, or recipients of solid organ or stem cell transplantation. The type and degree of the immune defect dictates the profile of potential opportunistic pathogens; T-cell-mediated defects increase the risk of viral (cytomegalovirus [CMV], respiratory viruses) and *Pneumocystis jirovecii* (PJ) infections, whereas neutrophil defects are associated with bacterial pneumonia and invasive aspergillosis. However, patients often have combined immune defects, and a wide range of other opportunistic infections can cause pneumonia [4-6]. Importantly, conventional non-opportunistic pathogens are frequently found in immunocompromised hosts and should not be overlooked. The radiological pattern of disease (best assessed by CT scan) and the onset speed help identify the likely pathogen(s); this can then be supported by targeted investigation including the early use of bronchoscopy in selected patients. Rapid and expert clinical assessment can identify the most likely pathogens, allowing timely appropriate therapy.

Opportunistic infections occur when the loss of adequate innate or adaptive immune responses allows a normally low-virulent organism to cause infection. The type and degree of the immune defect dictate the profile of potential opportunistic pathogens. For example, prolonged high-dose glucocorticoids (>20 mg/day for >21 days) and calcineurin inhibitors predispose to *Pneumocystis jirovecii* pneumonia (PJP); biological agents prescribed for immuno-mediated diseases are associated with specific immune defects that increase the risk of opportunistic lung infections (such as those of tumour necrosis factor-α [TNFα] inhibitors and risk of mycobacterial disease, endemic fungi and *Legionella pneumophila*; or anti-CD20 drugs and mycobacterial disease, CMV pneumonitis and PJP). Common infections in otherwise healthy individuals should not be forgotten as they can cause infection in immunocompromised hosts. Opportunistic lung infections are a major cause of morbidity and mortality in patients who are immunocompromised by non-treated HIV infection, haematological malignancies, aplastic anaemia or chemotherapy treatment, as well as those recipients of solid organ or stem cell transplants. Opportunistic infections can also hinder the treatment with new biological therapies for inflammatory or immune-mediated conditions. Expert clinical assessment, early diagnosis, and aggressive treatment are required for a positive outcome. CT is more sensitive than thorax radiography in order to define the predominant pattern(s) of lung involvement. When combined with knowledge of the patient's immune status (loss of T-cell- or antibody-mediated immunity, or defects in neutrophil-mediated immunity), it often identifies the most likely pathogens.

Several recent review articles provide a concise overview and focus of the most common opportunistic lung infections in immunosuppressed patients [7-10].

IMAGING TECHNIQUES IN THE DIAGNOSIS OF PULMONARY ALTERATIONS IN IMMUNOCOMPROMISED PATIENTS

CT thorax scans are preferred over chest X-rays to define the radiological pattern of disease in immunocompromised hosts. Chest CT and the microbiological analysis of biologic

specimens are the first line diagnostic tools in immunosuppressed hosts. Sometimes, invasive methods are also mandatory. Image interpretation requires a complete assessment of the often-complex clinical context. Some key clinical and radiological aspects make it possible to orient the diagnosis correctly and to understand the current role of CT in the therapeutic strategy. Performing chest CTs in immunosuppressed patients pursues two objectives: early detection of lesions requiring urgent treatment not visible in the chest X-rays, and better characterization of findings to outline diagnostic and therapeutic possibilities. Reconstructions with slice thickness <1.5 mm of high-resolution computed tomography (HRCT) are required since many of the pulmonary complications present with interstitial patterns.

Therefore, chest HRCT plays a fundamental role. It must be urgently performed if there are clinical signs of severity in the first 24h, or in the absence of a response to antibiotics therapy in 72-96h, when invasive fungal infections (IFI) must be considered to initiate early antifungal treatment, a determinant prognostic factor. In patients clinically classified as being in high risk of IFI, antifungal drugs must be empirically administered. However, in lower risk subgroups, therapeutic delay can be acceptable in cases of very likely clinical manifestations or early positive specific infection biomarkers, which reduces the high costs and toxicity of these drugs. Serum galactomannan antigen test and beta-D- glucan detection are the fungal biomarkers usually used, and the chest HRCT is early performed early. However, galactomannan, a component of the *Aspergillus* cell membrane, is falling into disuse as a fungal biomarker due to its diminished sensitivity associated to antifungal prophylaxis strategy. In patients under antifungal prophylaxis, the galactomannan antigen test is more profitable when performed in BAL. The performance of a HRCT scan becomes even more important as an urgent diagnostic test that allows early antifungal therapy when IFI-compatible lesions are visualized. In addition, it can suggest other possible aetiologies and guide the acquisition of BAL through bronchoscopy, thus speeding up the diagnosis of germs not covered by the initial empirical therapy. In other respiratory manifestations HRCT is also necessary to identify and characterize non-infectious complications, relapse, and secondary neoplasms that can go unnoticed in radiographic tests or show similar patterns.

When studying the HRCT of an immunocompromised patient, a complete knowledge of the clinical context and the underlying condition, treatment, and complications is crucial. Treatment-induced non-infectious pulmonary complications (aggressive chemotherapy and, in certain cases, solid organ or hematopoietic precursors transplantation [SOT or HPT]) are also frequent and determine prognosis. Pulmonary tumour disease includes infiltration due to haematological or metastatic solid neoplasms, primary pulmonary neoplasm, and post-transplantation lymphoma. Chemotherapeutic drugs do not only depress immune function, but some of them are responsible for pulmonary toxicity. It can be suspected by the radiologic pattern and its temporal relation with the treatment. Other therapeutic agents can cause respiratory failure, often presenting with a radiologic expression similar to alveolar damage, oedema, or haemorrhage.

In a didactic and summarized way, the main key pulmonary radiological findings that can be found in the differential diagnosis of infectious and non-infectious causes of pulmonary infiltrates are the following [11]:

- Nodes and masses (infections, pulmonary infiltration due to hematologic neoplasms, secondary neoplasms)
- Cavitations (fungal, mycobacterial, and bacterial infections, lymphoma, histiocytosis, etc.)
- Areas of attenuation in ground glass, consolidations, or opacities (infections, disease non-infectious complications, non-infectious complications secondary to treatment)
- Budding tree images (these images represent bronchioles filled with mucous, liquid or pus. They usually correspond to an infectious bronchiolitis that can be due to many different microorganisms)
- Bronchial wall thickening (it can be due to unspecific respiratory infection, smoking, *bronchiolitis obliterans*, lymphoid infiltration, or other bronchial conditions)
- Peri-lymphatic interstitial thickening
- Obstructive bronchial lesions
- Air entrapment areas
- Pulmonary fibrosis (it can be secondary to distress, toxicity of chemotherapy, infection, or radiotherapy, or correspond to an unclassifiable interstitial pneumonia or to a graft-versus-host disease (GVHD)-related pleuro-parenchymatous fibroelastosis)
- Bronchial dilations (they can be seen in a transitory way in the sinus of infectious consolidations and in organizing pneumonia; irreversible dilations [bronchiectasis] in areas of air entrapment are a characteristic finding of *bronchiolitis obliterans* unlike those observed in areas of fibrosis due to traction)
- Interstitial pulmonary emphysema -air leak syndrome- (it is a typical complication of advanced post-HPT *bronchiolitis obliterans* and a marker of poor prognosis)
- Spontaneous pneumothorax
- Pulmonary cysts (small cysts in the upper fields can correspond to pneumatoceles due to infection by PJ; bilateral cysts, isolated or associated with nodes and lymphadenopathies should make us think of the possibility of a pulmonary disease due light chains deposit disease in patients with multiple myeloma or macroglobulinemia and obstructive functional pattern)

Regarding the follow-up of pulmonary lesions, periodical repetition of HCRT scan is recommended in patients with fever and documented infection until resolution of the findings:

In cases of good clinical response, it is possible to wait for several weeks and even for 1 or 2 months (the estimated resolution time of the findings). During the first week of treatment, worsening of IFI lesions is not usually related to a poorer

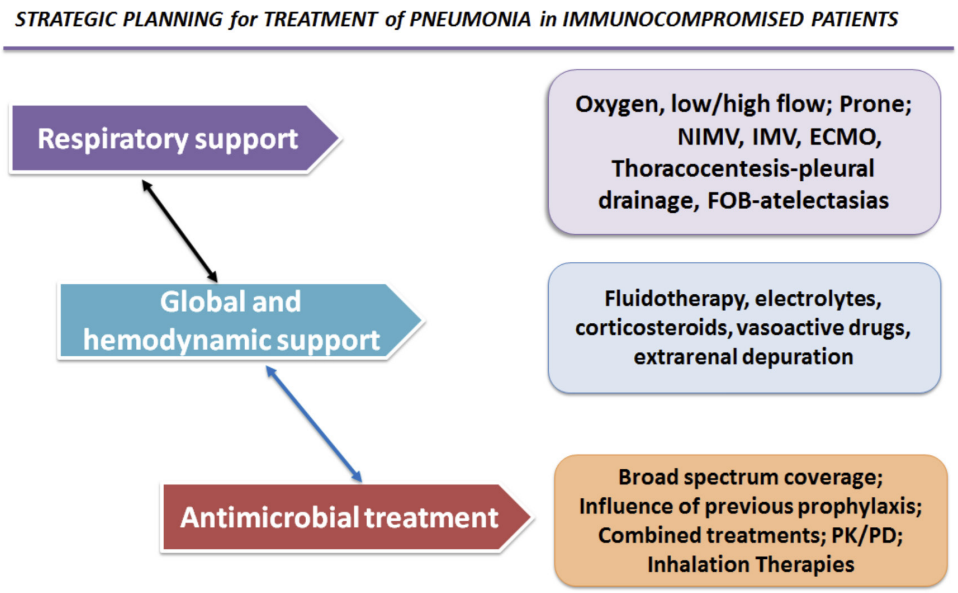

Figure 2 Strategic planning for treatment of pneumonia in immunocompromised patients

FOB: fibreoptic bronchoscopy; IMV: invasive mechanical ventilation; NIMV: Noninvasive mechanical ventilation; PK/PD: pharmacokinetics/pharmacodynamics.

evolution (paradoxical response). Moreover, in all infections, immune-reconstitution syndrome (IRS) must be conveniently recognized so as not to be taken as an absence of response. IRS is expressed as an inflammatory exacerbation secondary to neutrophil recovery or to the withdrawal of immunosuppressant therapy which, in turn, translates into clinical worsening and lesion growth.

Suspecting a lack of response (due to clinical and/or radiographic findings worsening), it is important to repeat the diagnostic tests to rule out initially unidentified mixed infections or other underlying or *de novo* processes that involve serious pulmonary complications (such as *bronchiolitis obliter*ans, GVHD, idiopathic pneumonia syndrome, or interstitial lung disease) [12].

In immunosuppressed patients, thorax HRCT scanning aids in the differential diagnosis of infectious and non-infectious pulmonary complications by integrating image findings and clinical data. Furthermore, it needs to be promptly performed in cases of acute clinical symptoms and suspicion of IFI. It will allow the assessment of treatment response, detection of malignancy, and optimization of BAL or lung biopsy sampling [13].

MANAGEMENT OF THE SEVERELY IMMUNOCOMPROMISED CRITICALLY ILL PATIENT

A large group of severely ill immunocompromised patients become critically ill patients. The proportion of critical patients with a deficient immune system has recently risen up to a third of all intensive care unit (ICU) admissions. Immunocompromised patients include patients receiving long-term (> 3 months) or high-dose (> 0.5 mg/kg/day) steroids or other immunosuppressant drugs, SOT recipients, patients with solid tumours requiring chemotherapy in the last 5 years, or with haematological malignancies independently of its diagnosis and therapeutic strategies, as well as patients with primary immune deficiencies (PID). In the last two decades, ICU admissions of patients with HIV/AIDS infection and severe infectious pulmonary lesions have largely decreased due to the extension of effective and early antiretroviral treatment. Other factors contributing to this trend include the increased aggressiveness and duration of cancer treatments, greater use of organ and hematopoietic cell transplantation, and introduction of steroid sparing agents for the treatment of autoimmune and autoinflammatory diseases. Thus, a large number of patients are now expected to live for many years with immune deficiencies that put them at risk for severe infections.

Severe respiratory infections are the leading reason for ICU admission in immunocompromised patients [14], who are at risk for hypoxemic acute respiratory failure (ARF) and sepsis. Life-supporting interventions must be implemented simultaneously to investigations directed to identify the cause of the pulmonary involvement (Figure 2). In these patients, lack of definite aetiological diagnosis is related to increased mortality rates. Moreover, specific pathogen identification is crucial for antimicrobial stewardship. However, the aetiological diagnosis can be extremely challenging, as the effects of the infection

Table 2 The DIRECT approach to acute respiratory failure in immunocompromised patients*

D. Delay: time since respiratory symptoms onset; since antibiotic, antiviral or antifungal prophylaxis or treatment; since transplantation; since the diagnosis of malignancy or inflammatory disease
I. Immune deficiency: knowledge on the nature of immune defects and ongoing antibiotic, antiviral or antifungal prophylaxis will help avoiding missing opportunistic infections
R. Radiographic appearance: A chest radiograph will not only report the extent and patterns of pulmonary infiltrates (consolidation, air bronchogram, nodules, cavitations, tree in bud, interstitial pattern...), but also the presence and importance of pleural effusion, mediastinal mass, cardiomegaly, pericarditis, etc
E. Experience: clinical experience of the ICU team and specialist consultants with this type of patients (treatment-related toxicity, viral reactivation, atypical form of diseases, cardiac involvement, graft versus host disease, obliterans bronchiolitis, etc.)
C. Clinical picture: the presence of shock is likely to be associated with bacterial infection, but may be seen in hemophagocytic lymphohistiocytosis, toxoplasmosis, disseminated miliary tuberculosis, adenoviral infections, HHV6 reactivations or severe SARS-CoV-2 infection. Similarly, absence of fever or presence of tumoral syndrome (liver, spleen, and lymph nodes) will be considered as a possible orientation
CT scan provides a better description of the radiographic patterns and guides the diagnostic strategy towards non-invasive or invasive diagnostic tests

*** Adapted and modified from reference 8**

combine with those of the underlying disease and treatments to create extraordinarily complex clinical pictures.

In addition, some patients have more than one concurrent infection, and others have non-infectious causes of ARF that mimic infection. Furthermore, fibreoptic bronchoscopy and bronchoalveolar lavage (FOB/BAL) are commonly used for diagnosis [15], but may cause further respiratory deterioration in patients with hypoxemia. The development of non-invasive diagnostic tests with high sensitivity and specificity (e.g., on blood, plasma, sputum, urine, or nasal swabs) has obviated the need for FOB/BAL in some patients. The utility of these non-invasive tests is being evaluated, and will hopefully provide clinicians with additional tools in the diagnosis of these complex patients.

ARF in an immunocompromised patient may be due to infection by more than one viral, bacterial, fungal, or parasitic agent. In addition, non-infectious factors may contribute to cause ARF and should be routinely sought. These factors, which are simply enumerated but not discussed in this review, include radiation, drug-related pulmonary toxicity, diffuse alveolar haemorrhage, pulmonary oedema, and lung lesions due to the underlying disease (e.g., leukemic infiltrates, engraftment syndrome, GVHD, lymphangitic carcinomatosis, and pulmonary vasculitis, among others). Existing guidelines for managing lung disease in critically ill immunocompromised patients emphasize the importance of obtaining valid diagnostic samples [16]. However, antimicrobial therapy is often started immediately, before samples are collected. As a result, causative pathogens are only identified in approximately half the patients with bacterial pneumonia. A detailed analysis of the clinical, laboratory, and imaging findings can provide a valuable diagnostic orientation in these cases. Nevertheless, the frequency of bacterial pneumonia is probably underestimated, as many cases are atypical and, therefore, escape recognition. Apart from infectious agents, non-infectious pulmonary abnormalities may be mistakenly diagnosed as clinically documented infections. Pulmonary side-effects from cytotoxic drugs, radiotherapy or pulmonary involvement by the underlying malignancy should be included into differential diagnosis and eventually be clarified by invasive diagnostic procedures.

The basic rules described in certain reference publications [8] provide a helpful guidance for determining the cause of pulmonary infiltrates and selecting appropriate diagnostic strategies. In immunocompromised patients with ARF, the first step in the aetiological evaluation is an accurate clinical assessment. The authors of this review advocate the use of the mnemonic DIRECT (Table 2) based on the following data: days since respiratory symptoms onset, type of immunodeficiency, radiographic pattern, experience of the assessing clinician, clinical findings, and high-resolution computed tomography (HRCT) findings. Most of these variables are easily evaluated at the bedside, and their analysis usually restricts the number of possible aetiologies to two or three. Additional invasive and non-invasive investigations should be performed as needed. The diagnostic strategy should be tailored to the pretest probability of the disease being sought. Importantly, the indications of FOB/BAL are changing to avoid exposing patients to unnecessary potential adverse events. When FOB/BAL is considered as mandatory, it should be performed under optimal monitoring and high-flow oxygen therapy should be used to correct hypoxemia. The risk for intubation should be assessed carefully as it is associated with higher mortality. The introduction of non-invasive tests, notably those based on next-generation sequencing (NGS), transcriptomics, and proteomics, may reduce the need for FOB/BAL.

Pre-emptive treatment with mold-active systemic antifungal agents improves clinical outcomes, while other microorganisms are preferably treated only when microbiologically documented. High-dose trimethoprim/sulfamethoxazole is the first-choice agent for the treatment of PJP. CMV pneumonia is treated primarily with ganciclovir or foscarnet in most pa-

tients, assessing the possibility of specific intravenous immunoglobulins in alo-HTP receptors [17]. In a considerable number of patients, clinical outcomes may be favourable despite ARF. Hence, intensive care should be unrestrictedly provided in patients whose prognosis is not desperate due to other reasons.

SUMMARY AND CONCLUSIONS

The management of immunocompromised patients with diffuse pulmonary infiltrates remains a common and recurrently difficult problem with a wide range of range of diagnostic possibilities. Non-invasive diagnostic procedures are of low utility, and the drugs available for empiric therapy have sometimes severe toxic effects. Although guidelines for management have been developed, they may be predicated on data from a single institution or depend on diagnostic procedures and laboratory facilities not necessarily available to physicians in all locations.

The increase in survival in patients with cancer and immune-mediated inflammatory diseases is paralleled by an increase in the frequency of critically ill immunosuppressed patients with severe infections. Severe bacterial pneumonias, followed by viral, fungal, and more rarely, parasitic infections are the leading cause for acute hypoxemic respiratory failure in these patients. When ICU admission is needed, mortality rates are high. Knowledge of the underlying immune deficiency and a complete clinico-radiological evaluation can guide the diagnostic strategy by targeting the most likely infectious agents and deciding on invasive versus non-invasive approaches. Increasingly sophisticated non-invasive diagnostic tools entailing lower morbidity than invasive techniques and are now available or under evaluation (e.g., real-time PCR, next-generation sequencing, and transcriptomics). These tools might allow an earlier diagnosis and thus improve survival in immunocompromised patients with severe pulmonary infections.

Controversy still exists regarding whether making a definitive diagnosis in these patients has an impact on the overall outcome. An individualized approach must take into consideration local resources, patient's age and prognosis, type of immunosuppression, family and patient's opinions regarding the use of invasive measures and heroic support, and previous patterns of infection in the institution. Invasive procedures should only be performed if a specific therapeutic management is expected to change based upon results.

CONFLICT OF INTERESTS

The authors declare no conflict of interest in relation to this article.

MS has given lectures and participated in advisory boards under the auspices of various companies (Angelini, Gilead, MSD, Pfizer, Shionogi) in the last year.

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Diagnostic and therapeutic approach to fungal pneumonia in the critically ill patient

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ABSTRACT

Aspergillus spp. is the fungus most frequently producing ventilator-associated pneumonia (VAP), constituting 8% of them. This risk is significantly increased in onco-hematological patients: solid organ transplant recipients, chronic obstructive pulmonary disease (COPD), corticotherapy, cirrhosis, solid cancer, or viral pneumonias. The European Organization for Research and Treatment of Cancer Mycoses (EORT/MSG criteria) developed for onco-hematological patients with angioinvasive forms of aspergillosis have important limitations for broncho-pulmonary forms, such as aspergillosis cases in the ICU. In recent years, new diagnostic criteria were developed to have a greater role in broncho-alveolar lavage, especially GM and lateral flow assay (LFA). Voriconazole and isavuconazole are the first treatment option. However, drug-drug interaction, level requirements, toxicity, and QT-interval modification are limitations that may favor isavuconazole or liposomal amphotercin B in the ICU.

Keywords: Aspergillus, broncho-alveolar lavage, voriconazole, isavuconazole

EPIDEMIOLOGY OF FUNGAL PNEUMONIA IN THE INTENSIVE CARE UNIT

Ventilator-associated pneumonia (VAP) is the most frequent infection in patients admitted to the intensive care unit (ICU), usually occurring in one third of them. According to the latest national surveillance study of nosocomial infection in ICUs in Spain [1], *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Staphylococcus aureus* are the etiologic agents most frequently implicated, as all of them produce 44% of VAP [1]. In this registry, 10% of VAP are of fungal origin, mainly caused by Aspergillus sp. which accounts for 8% in ICU patients [1]. The role of other molds is anecdotal: zygomycosis infections are currently restricted to patients with hematological malignancies, primarily with prolonged neutropenia and solid organ transplanted patients with a degree of immunosuppression. In contrast, there has been a significant decrease in recent years in diabetic ketoacidosis as a zygomycosis risk, associated with improved management of diabetes in the general population [2]. Infections from agents such as *Fusarium, Scedosporium,* and *Lomentosphora,* while other molds are limited to prolonged neutropenias and similar behavior to invasive aspergillosis. *Pneumocystis jirovecci* pneumonia, restricted to patients with cellular immunosuppression and endemic fungal infections (*Histoplasma* spp. and others) are in certain geographical areas, and need special consideration.

Candida spp. as a causative agent of VAP is controversial. Some authors exclude it as an etiological agent and others estimate its incidence below 1%, related to risk factors such as severe immunosuppression, malnutrition, high fungal load (e.g., diabetes, alcoholism, gastroesophageal reflux, presence of esophageal diverticula), or broad-spectrum antibiotic therapy [3]. Regardless of causality, a recent meta-analysis associated airway colonization by *Candida* spp. in ICU patients with a longer duration of intubation, higher ICU mortality, and a higher 28-day mortality rate [4].

RISK FACTORS FOR INVASIVE PULMONARY ASPERGILLOSIS (IPA) IN ADMISSIONS TO THE ICU

By the number of patients, ICU admission alone is the largest risk factor for IPA, above classic factors such as the onco-hematologic patient or transplant recipients, as they comprise most IPA diagnoses in a general hospital [5].

Bassetti et al. categorized patients in the ICU according to IPA risk (Table 1) [6]. Isolation of *Aspergillus* spp. in respiratory

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specimens is associated with high mortality in the critically ill patient. Invasive forms can be associated with mortality between 69-77%, but colonization in the absence of infection is also associated with a mortality of 38%, as demonstrated in a recent study on 563 patients from 30 ICUs in eight countries [7]. The following independent mortality factors were observed: age, hematopoietic progenitor transplantation, mechanical ventilation, high SOFA score (Sequential Organ Failure Assessment) and dialysis at diagnosis – which are associated with invasion vs. colonization in cancer patients (including hematologic) or solid organ transplantation [7].

Patients with severe chronic obstructive pulmonary disease (COPD) receiving broad-spectrum antibiotics and corticosteroids are becoming one of the main risk groups for IPA in ICU [8]. Guinea et al. analyzed the risk of IPA in COPD patients and confirmed the following: admission to the ICU, chronic heart failure, antibiotic treatment in the 3 months prior to admission, accumulated dosage of corticosteroids equivalent to > 700 mg prednisone in the 3 months prior to admission, and a similar accumulated dosage of corticosteroids from admission to the first clinical isolation of *Aspergillus* [8].

Table 1 Risk Factors for IPA in ICU Patients

1. High risk
Neutropenia (500/mm^3)
Hematological malignancy
Allogeneic HSCT
2. Intermediate risk
Prolonged treatment with corticosteroids before admission to the ICU
Autologous HSCT
COPD
Liver cirrhosis
Solid organ cancer
HIV infection
Lung transplantation
Systemic immunosuppressive therapy
3. Low risk
Severe burns
Solid organ transplant
Steroid treatment for > 7 days
Prolonged stay in the ICU (> 21 days)
Malnutrition
Post cardiac surgery
Near drowning

COPD chronic obstructive pulmonary disease, HIV human immunodeficiency virus, HSCT hematopoietic stem cell transplantation, ICU intensive care unit, and IPA invasive pulmonary aspergillosis. Modified from reference [6].

The use of certain biologics is associated with an increased risk of IPA in clinical practice; in recent years, this includes ibrutinib –used to treat chronic lymphocytic leukemia, mantle lymphoma, and Waldestrong's disease; an elevated risk of IPA was observed when used in combination or after other immunosuppressive treatment, especially Janus kinase inhibitors (JAK) (ruxolinitib) or idelalisib [9].

Controversy exists about ECMO (extracorporeal membrane oxygenation) as a risk factor for IPA in ICU patients. Some studies attribute a 7% risk of IPA to ECMO patients [10]. However, a study conducted in over 20,000 patients in 300 centers in the American Extracorporeal Life Support Organization Registry found that 1.4% was the risk of IPA among ECMO patients, higher in onco-hematology, solid organ transplantation, or influenza [11].

In recent years, certain respiratory viral infections, such as influenza or SARS-CoV-2, appear as important risk factors for IPA. A study performed in 7 ICUs in Belgium and the Netherlands, confirmed an incidence of IPA in 19% of those admitted with influenza to the ICU; this reached 32% in immunocompromised patients, with an associated overall mortality of 51% [12]. Coinciding with the SARS-CoV-2 pandemic, an increased incidence of IPA is described, especially in patients admitted to the ICU, estimated at 20-35% in certain national series [13].

DIAGNOSIS OF *ASPERGILLUS* PNEUMONIA: PECULIARITIES OF THE CRITICALLY ILL PATIENT

Regardless of the type of clinical form or baseline condition, documentation of hyphae on biopsy, or isolation of *Aspergllus* spp. in a culture of a sterile specimen constitutes a diagnosis of proved infection. However, this can only be confirmed in a minority of patients**.**

The positive predictive value of *Aspergillus* isolation in sputum is generally low, depending on patient type and risk; it may not exceed 10% in COPD patients, or even reach 50% in liver transplant recipients, or exceed 80% in hematopoietic stem cell transplant patients. The EORTC and Mycoses study groups (MSGs) developed well-validated criteria in onco-hematological patients [14,15]. As such, a diagnosis of probable aspergillosis includes the intersection of 3 factors: a) host at risk (e.g., prolonged neutropenia, GVHD, or solid organ transplantation), b) image: the presence of at least one of the following four patterns: dense, well-circumscribed lesions with or without a halo sign, air crescent sign cavity, wedge-shaped and segmental, or a lobar consolidation, and c) microbiologic: Aspergillus spp. isolation in respiratory samples, a positive galactomannan (GM) in serum or bronchoalveolar lavage (BAL), or a positive direct test (cytology, direct microscopy). Positive PCR was not considered diagnostic of IPA in previous consensus criteria [14] but was incorporated in the last version [15]. The presence of only 2 factors: a) host and b) image, in the absence of a microbiological confirmation, can only be considered possible invasive fungal infection.

Application of these criteria to a patient admitted to the

Table 2 **Algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients**

Proven Invasive Pulmonary Aspergillosis Idem EORTC/MSG criteria
Putative Invasive Pulmonary Aspergillosis **(All four criteria must be met):**
1. *Aspergillus*-positive lower respiratory tract specimen culture (= entry criterion)
2. Compatible signs and symptoms (one of the following): *Fever refractory to at least 3 d of appropriate antibiotic therapy *Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause, pleuritic chest pain *Pleuritic rub *Dyspnea *Hemoptysis *Worsening respiratory insufficiency despite appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT lung scan
4. Either 4a or 4b
4a. Host risk factors (one of the following): *Underlying hematological / oncological malignancy treated with cytotoxic agents *Neutropenia (absolute neutrophil count, 500/mm^3) preceding or same time as ICU admission *Glucocorticoid treatment (prednisone equivalent, > 20 mg/d) *Congenital or acquired immunodeficiency
4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid, without bacterial growth, together with a positive cytological smear showing branching hyphae
Aspergillus respiratory tract colonization If more than 1 criteria are missing for a diagnosis of putative IPA, the case is classified as Aspergillus colonization

Definition of abbreviations: BAL: bronchoalveolar lavage; CT: computed tomography; EORTC/MSG: European Organization for the Research and Treatment of Cancer/ Mycosis Study Group; ICU: intensive care unit. Modified from reference [19].

ICU is challenging. Different studies confirmed that the sensitivity of these criteria decreases significantly in non-onco-hematological patients; in these patients, according with a bronchopulmonary origin, the most frequent radiological infiltrates are peribronchial consolidation or a tree-in-bud pattern, differing from the typical signs observed in onco-hematological patients (re: halo sign or air crescent sign cavity) [16].

In addition to low specificity of IPA infiltrates in the non-onco-hematologic patient is the lower cost-effectiveness of serum GM with bronchopulmonary forms of IPA, the case with most ICU patients. Serum GM has a lower sensitivity in patients with immunosuppressive conditions and in COPD patients vs. hematological patients. We previously confirmed a sensitivity of only 56% in the diagnosis of IPA in liver recipients [17], with a sensitivity < 50% reported in a systematic review of the literature for non-hematology–oncology patients [18].The value of serum GM in patients with COPD, and risk of IPA, was evaluated in several studies, with sensitivity ranging between 30% and 60% [18]. Reduced sensitivity has been linked to two factors: increased clearance of GM by circulating neutrophils and lower angio-invasiveness of *Aspergillus* spp. [18].

To overcome these problems in ICU patients, new criteria for probable or putative aspergillosis are proposed (AspICU) and extensively validated in prospective cohorts [19] (Table 2). These criteria require a 'sine qua non' condition or isolation of *Aspergillus* spp. in respiratory samples (sputum or broncho-aspirated sample). Thereafter, for AspICU criteria, the following combination was required: a) compatible signs and symptoms, b) abnormal medical imaging by portable chest X-ray or CT scan of the lungs (not limited to accepted in onco-hematologic patients), and c) host risk factors or positive cytological smear. For diagnosis of tracheobronchitis, the presence of tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar on a bronchoscopic analysis with visualization of hyphae in biopsy or isolation of Aspergillus in culture, is required [19].

These discrepancies in diagnostic criteria led to considerable confusion in ICU patients. The description in recent years of IPA in patients with influenza, and more recently in patients infected by SARS-CoV-2, allowed these diagnostic criteria to be reevaluated. Table 3 shows criteria applied for diagnosis of IPA with influenza (IAPA) for patients admitted to the ICU [20]. These criteria, as in AspICU criteria, accept the presence of "pulmonary infiltrates" without specificity of EORTC/MSG infiltrates (halo sign, air crescent sign cavity...). To acquire specificity, it is compensated with a more demanding microbiological criterion, such as isolation of Aspergillus spp. or a GM > 1.0 in BAL, or the presence of positive GM in blood (> 0.5); yet, as already mentioned, this technique is not sensitive in non-onco-hematological patients [20]. In the absence of BAL, the iso-

Table 3 Proposed case definition for IAPA in ICU patients

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	Aspergillus tracheobronchitis	IAPA in patients without documented *Aspergillus* tracheobronchitis
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue
Probable	Airway plaque, pseudomembrane or ulcer and one of the following: Serum GM index > 0.5 or BAL GM index ≥ 1.0 or Positive BAL culture or Positive tracheal aspirate culture or Positive sputum culture or Hyphae consistent with *Aspergillus*	A: Pulmonary infiltrate and at least one of the following: Serum GM index > 0.5 or BAL GM index ≥ 1.0 or Positive BAL culture OR B: Cavitating infiltrate (unattributed to another cause) and at least one of the following: Positive sputum culture or Positive tracheal aspirate culture

Modified from reference [20]

lation of *Aspergillus* in sputum, tracheal aspirate, or bronchial aspirate (sample with a higher risk of colonization) is compensated by a pulmonary infiltrate of IPA, such as cavitary infiltrate, which would not be justified with any other cause [20].

In the absence of characteristic radiological images, most diagnostic criteria in the ICU and non-onco-hematological patients employs the bronchoalveolar lavage, primarily GM in BAL, as the principal tool for IPA diagnosis. In a recent multicenter study to analyze the role of GM in bronchoalveolar lavage fluid for diagnosis of IPA in non-hematological patients including ICU and COPD patients a global sensitivity of BALF GM (optical density index [ODI] ≥ 1.0) of 77.4% was confirmed; sensitivity was higher in patients with immunosuppressive conditions than those with COPD (81.8% vs 66.7%; p: 0.38) [16]. In COPD patients, the best performance was obtained for BALF GM (ODI ≥ 0.5). The sensitivity of GM in serum was very poor in both populations (36.4% and 11.6%, respectively) [16].

The recently published criteria for IPA in patients with SARS-CoV-2 infection (CAPA) include the same criteria as IAPA for proven and probable aspergillosis, although for probable aspergillosis, they also consider diagnostic criteria as the visualization of hyphae on BAL cytology (or fungal stain) and PCR amplification of Aspergillus spp. in blood (x2) or BAL, provided that such amplification occurs in advance of cycle 36 [21]. In addition, the CAPA criteria also include a category of possible aspergillosis that maintains the same clinical and imaging criteria as probable aspergillosis, but it allows for a microbiological "non-bronchoscopic lavage" specimen [21]. The visualization of hyphae in non-bronchoscopic lavage, or in isolation in culture or a high titer (> 4 GM), or > 2 for a determination when accompanied by isolation in culture - are all considered diagnostic. Detection of GM in non-bronchoscopic lavage is seen as evidence of CAPA; on the other hand, proposed cutoff values are based on a single study and need further validation [22]. Authors propose that although classification of possible CAPA will likely be sufficient to initiate antifungal therapy, in line with other consensus statements, it is not recommended for enrolling patients in clinical trials [21].

Lateral flow devices (LFD) to detect fungal antigens are not novel [23,24]. The first LFD for IA was described in 2008 but generated pooled sensitivity and specificity [23]. The recent release of the IMMY Sona Aspergillus GM lateral flow assay (LFA) incorporates two monoclonal antibodies (Mab), one novel Mab and one targeting a similar GM epitope to the Bio-Rad Platelia Aspergillus Antigen Assay (Hercules, CA, USA), has the potential to improve performance as demonstrated with cryptococcal LFD [23]. Comparison to the OLM LFD when testing BAL fluid showed the LFA as providing significantly better sensitivity (83% vs. 69%, p = 0.008), while maintaining specificity (87%) for proven or probable IPA [23]. An automated digital cube reader for quantification of results was recently added to the test kits. Diagnostic performance of the LFA is improved when utilizing a higher cutoff of 1.0 or 1.5 ODI, vs. the currently recommended cutoff of 0.5 ODI, which showed limited specificity [24].

IPA THERAPY IN ICU

We recommend either voriconazole or isavuconazole as first-line treatment for possible, probable, or proven aspergillosis in the ICU patient. Since Herbrecht's study [25], all guidelines include voriconazole as the first option; however, the critically ill patient has some characteristics that may limit its use, or the possibility of interactions with other drugs metab-

Table 4 Comparative inhibition of selected CYP450 isoenzymes by triazoles

Azole	CYP2C8	CYP2C9	CYP2C19	CYP3A4
Fluconazole	++	++	+	++
Itraconazole	+	+	-	+++
Voriconazole	++	++	+++	++
Posaconazole	-	-	-	+++
Isavuconazole	-	-	-	+/++

Notes: -, no inhibition; +, mild inhibition; ++, moderate inhibition; +++, strong inhibition.
Modified from reference [30].

olized at the cytochrome p450 level, despite the need to have levels available, given the frequency with which voriconazole cannot reach therapeutic levels. This makes isavuconazole or liposomal amphotericin B important alternatives in many patients in ICU. Voriconazole levels below 1 mg/L are associated with therapeutic failure in up to 46% of cases; response improves when this level is reached [26]. However, several studies, especially in the ICU, confirmed that approximately half the patients do not achieve serum therapeutic levels [27]. This difficulty with voriconazole occurs even with its intravenous formulation, as related to the individual-dependent bioavailability characteristic of this drug. Yet, the therapeutic range of voriconazole is narrow and serum levels > 5 mg/L are associated with hepatic and encephalopathic toxicity [26]. The presence of high levels has been documented in the ICU in up to 10% of patients.

The SECURE study conducted mainly in onco-hematological patients, but not including critically ill patients, confirmed the non-inferiority of isavuconazole vs. voriconazole in IPA, but with a significant reduction in hepatic, cutaneous, and ocular toxicity [28]. A recently published randomized, double-blind study also confirmed the non-inferiority of posaconazole to voriconazole, mainly in onco-hematological patients [29]. In the case of posaconazole, in addition to intravenous administration, the oral tablet formulation also significantly improved the pharmacokinetics and absorption of the oral solution formulation [29]. Among the three azole drugs mentioned, isavuconazole has a lower degree of interactions, conferring a substantial advantage in the critically ill patient [30]. Isavuconazole is a moderate CYP3A4 inhibitor, while other azoles, especially voriconazole, in addition to inhibiting CYP3A4, also inhibit CYP2CB, CYP2C9, and CYP2C19 (Table 4). This indicates that the use of certain drugs, such as lopinavir, prednisone, estradiol, atorvastatin, or midazolam, do not require adjustment when administered with isavuconazole, only with voriconazole; others, such as cyclosporine, tacrolimus or sirolimus, where use may be contraindicated in the presence of voriconazole, they can be used with caution with isavuconazole [30]. Unlike other QT-prolonging azoles (voriconazole, posaconazole), isavuconazole reduces QT, favoring isavuconazole in the ICU. In favor of their use are post hoc results of the SECURE study, in which > 95% of patients receiving isavuconazole had levels > 1.5 mg/L, and determinations > 7 mg/L occurring in < 10%: these were not associated with increased toxicity, so except under special conditions, level monitoring was not required.

These arguments were also used by other authors to justify the use of liposomal amphotericin to the detriment of voriconazole. Garnacho et al. in a consensus of ICUs in Spain, justified the use of amphotericin B to the detriment of voriconazole in the management of aspergillosis in ICU patients, if the following circumstances were present: a) concomitant treatment with drugs metabolized by CYP3A4 or 2C9, b) treatment with drugs that can prolong QT, c) severe liver failure (Child C), or d) glomerular filtration rate < 50 mL/min [31].

Most guidelines advise against the use of combination therapy to treat invasive aspergillosis, due to lack of scientific evidence in published studies. In addition to *in vitro* and experimental studies, with diverse and contradictory results, the only prospective randomized clinical trial for a mainly onco-hematological population, analyzing the superiority of voriconazole and anidulafungin over voriconazole monotherapy did not confirm a significant reduction in mortality at 12 weeks, except in some subgroups [32]. In general, echinocandins are not recommended for use as monotherapy in primary invasive aspergillosis [20,21]. Despite this study, with some methodological limitations (long recruitment period and large number of losses, among others), many experts still consider the use of combination therapy in severe patients, especially given high expected mortality, such as ICU patients.

Optimal duration of therapy is unknown, as radiological lung imaging may not be a helpful tool, but the expert panel suggests 6-12 weeks as a treatment course. It seems reasonable to include follow-up lung CT imaging to document the resolution of infiltrates before termination of treatment. In patients who are immunocompromised, longer treatment might be necessary. Following the GM-index in serum as a measure of therapeutic response may be limited by its poor sensitivity if testing serum in non-neutropenic patients. However, follow-up respiratory samples, such as GM testing, could be useful in determining efficacy in patients who are GM-positive, which may similarly help determine treatment duration [20,21].

CONFLICTS OF INTEREST

Author declares no conflicts of interest

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Impact of vaccination on the epidemiology and prognosis of pneumonia

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ABSTRACT

Adults with lung diseases, comorbidities, smokers, and elderly are at risk of lung infections and their consequences. Community-acquired pneumonia happen in more than 1% of people each year. Possible pathogens of community-acquired pneumonia include viruses, pneumococcus and atypicals. The CDC recommend vaccination throughout life to provide immunity, but vaccination rates in adults are poor.

Tetravalent and trivalent influenza vaccine is designed annually during the previous summer for the next season. The available vaccines include inactivated, adjuvant, double dose, and attenuated vaccines. Their efficacy depends on the variant of viruses effectively responsible for the outbreak each year, and other reasons.

Regarding the pneumococcal vaccine, there coexist the old polysaccharide 23-valent vaccine with the new conjugate 10-valent and 13-valent conjugate vaccines. Conjugate vaccines demonstrate their usefulness to reduce the incidence of pneumococcal pneumonia due to the serotypes present in the vaccine.

Whooping cough is still present, with high morbidity and mortality rates in young infants. Adult's pertussis vaccine is available, it could contribute to the control of whooping cough in the most susceptible, but it is not present yet in the calendar of adults around the world.

About 10 vaccines against SARS-CoV-2 have been developed in a short time, requiring emergency use authorization. A high rate of vaccination was observed in most of the countries. Booster doses became frequent after the loss of effectiveness against new variants. The future of this vaccine is yet to be written.

Keywords: immunization, influenza, community acquired pneumonia, prevention, respiratory pathogens.

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INTRODUCTION

Lower respiratory tract infections are the 4th leading cause of death in the world according to the WHO [1]. Adults with lung diseases such as COPD, asthma, bronchiectasis, diffuse parenchymal lung diseases and diseases that target other organs (heart, kidneys, liver, immune system), smoking and neuromuscular diseases, are at risk of contracting lung infections and suffering its consequences, many of these infections can be prevented through vaccination.

In 2016, it was estimated that 336.5 million lower respiratory tract infections occurred in the world (32.2 per 100,000) [2]. In the US, community-acquired pneumonia (CAP) accounted for more than 4.2 million ambulatory care visits in 2016 and 1.3 million emergency department visits in 2017.

The US Centers for Disease Control (CDC) recommend vaccination throughout life to provide immunity. However, for various reasons, vaccination rates in adults are poor [3]. In this brief review we will review the vaccines of importance to the pulmonologist.

ETIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA

Knowledge of the etiology of this disease has changed over the last century in the same way that medicine in general has, going from limited knowledge to the discovery of the role of bacteria and respiratory viruses and their impact in the human being. In general, the most frequent aetiologies have evolved during the last 8 decades, on the one hand, from the appearance of new diagnostic methods that did not exist at the beginning of the 20th century, and on the other hand, from the impact of the use of the different antimicrobials, particularly for the treatment of bacterial infections. It all started with direct examinations and cultures of secretions normally free of pathogenic microorganisms such as blood, pleural fluid, and

Table 1 Etiology of community-acquired pneumonia in 2,329 adult patients

Microorganism	Cases per 10000 adults per year	Incidence/10000 per year (IC 95%)
Human rinovirus	2.0	(2.7-2,3)
Influenza A y B	1.5	(1.3-1.8)
Streptococcus pneumoniae	1.2	(1.0-1.4)
Metapneumovirus	0.9	(0.7-1.2)
Parainfluenza	0.8	(1.0-1.4)
Respiratory sincitial virus	0.9	(0.7-1.2)
Coronavirus	0.6	(0.4-0.7)
Mycoplasma pneumoniae	0.5	(0.4-0.7)
Staphylococcus aureus	0.4	(0.3-0.6)
Legionella pneumophila	0.4	(0.2-0.5)
Adenovirus	0.4	(0.2-0.5)

Nasal and oropharyngeal swabs were taken in 2,272 patients (98%), blood cultures in 2,103 (91%), and urinary antigen detection in 1,973 (85%). Some pathogen was found in 38% of the patients, including viruses in 27% and bacteria in 14%. Rhinovirus, influenza, and *S. pneumoniae* were the most frequent and the highest burden was observed in the oldest. Modified from Jain S, et al. [3].

various fluids and secretions. Then, the existence of bacteria that were not identified with current methods was recognized and agents such as respiratory viruses and "atypical" bacteria such as *Mycoplasma pneumoniae*, *Chlamydophyla pneumoniae*, *Legionella pneumophyla*, etc., began to be identified by serological methods or special cultures, not recognizable by current methods. Later, high-specificity urinary antigen tests appeared to detect recent infection by Legionella and pneumococcus. More recently, molecular studies such as polymerase chain reaction (PCR) have begun to be used for clinical diagnosis, which allows different viruses, bacteria, fungi, and parasites to be detected with very high sensitivity in different tissues and body fluids.

For this reason, the map of possible pathogens has now expanded significantly for both normal and immunosuppressed hosts. Jain et al. searching for the etiology of community-acquired pneumonia requiring hospitalization systematically using the available microbiological studies including the use of PCR in 2,320 individuals over 18 years of age, with radiologically confirmed CAP, they found that among the 12 main causes of acute pneumonia, 7 are viruses and that rhinovirus and influenza are more frequent than pneumococcus in this infection [4] (Table 1). In today's world, vaccines have been taking an increasingly important role in the prevention of respiratory infections. The health system of most countries in the world does not have a family doctor who is aware of most of the personalized care needs of a healthy or chronically ill individual, as is the case with pediatricians who perform their role in the care of healthy children, leading preventive measures and controlling the progress of the immunization schedule. In this sense, the pulmonologists sometimes function as "the adult's pediatricians", since in their routine visit, they must, among other things, review the immunization history of their patients.

A transcendental aspect that ranks the importance that vaccines aimed at preventing respiratory infections are occupying is the fact of the increase in life expectancy in the world. Thus, the percentage of people over 65 years of age was less than 20% in Latin America in 2015 and between 20 and 24% in Spain, but it is expected that by 2050 it will increase between 10 and 30% in Latin America, and more than 30% in Spain.

We will briefly review the salient aspects of the vaccines that the pulmonologist must handle.

INFLUENZA

This virus has in its structure a series of proteins and nucleic acids that are potential targets for the development of vaccines. It occurs annually in outbreaks of variable virulence that can occur between fall and spring. The virus poses ongoing challenges to vaccine development and vaccination strategies. The greatest interest is focused on the 17 subtypes of the hemagglutinin protein and the 10 subtypes of the neuraminidase that generate the theoretical possibility of having 170 different variants of the virus, each of which represents a significant change in the entity of the virus, and this change It manifests itself with the disappearance of the immunity that was sustained by another of these variants (antigenic shift). In addition, there may be minor changes that do not include the replacement of any of these proteins (antigenic drift). Howev-

Table 2 **Indications for influenza vaccination (CDC, ACIP).**

GROUPS WITH INCREASED RISK OF COMPLICATIONS
Severe maturational delay
Genetic syndromes and severe congenital malformations
Chronic respiratory conditions such as asthma, fibrocystic disease, COPD, bronchiectasis, etc...
Chronic heart diseases such as heart failure, etc...
Chronic renal, hepatic, hematological or metabolic pathology
Congenital or acquired immunosuppression (HIV, chemotherapy, or chronic corticosteroid (> 2mg Kg/day of prednisone or equivalent > 14 days), hematopoietic cell transplant, solid organ).
Neuromuscular diseases that affect secretion management.
Morbid obesity (>40 BMI)
Residents in nursing homes or long-term care institutions.
Advanced age
GROUPS THAT MAY TRANSMIT INFLUEZA TO HIGH-RISK PEOPLE
Health personnel
Employees in nursing homes or long-term care facilities.
Cohabitants of high-risk people,

Modified from CDC [5]

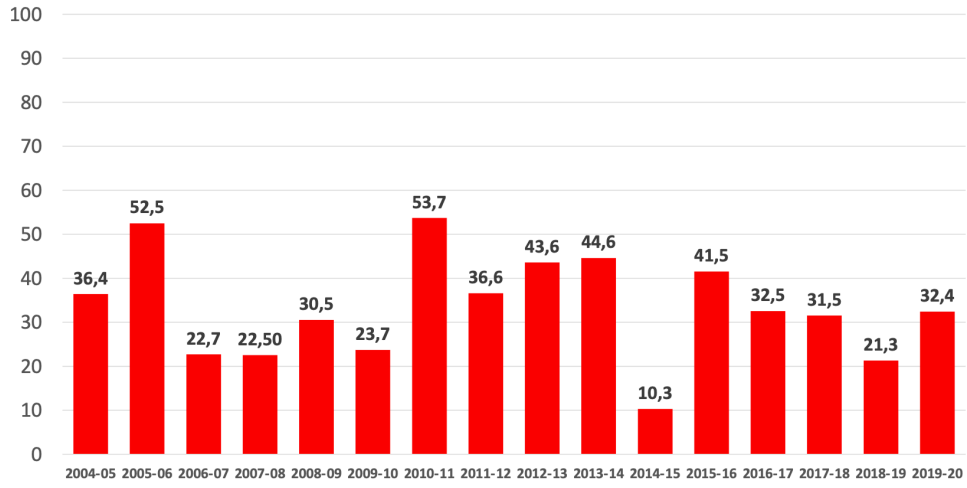

Figure 1 **Percentage of CAP due to pneumococcus according to the review of studies on the etiology of CAP published during the last century [7, 8].**

er, only 3 types of antigenic structures have been recognized so far in the virus (H1N1, H2N2 and H3N2), the drift is much more frequent and justifies the annual changes in the composition of the vaccine.

The vaccine available annually is developed considering the probable type of virus for the next influenza season during the summer of each hemisphere (north or south). At present, the conventional vaccine is trivalent (2 A viruses, lately H3N2 and H1N1) and the rest for influenza B. Currently, the quadrivalent vaccine that incorporated a second type of B virus is in use. Annual vaccination begins in the fall. There are inactivated vaccines with and without adjuvant for intramuscular or intradermal route, with double dose, and attenuated vaccine.

The indications of using this vaccine can change from country to country but in general they are similar throughout the world. Table 2 shows the indications according to the CDC [5].

The result of the vaccine is measured in 2 ways, the ideal is randomized clinical trials where the efficacy is measured in which one group receives the vaccine and the other the placebo; the other way is observational studies of effectiveness,

Table 3 Indications of anti-pneumococcal vaccination (CDC, ACIP).

GROUP WITH INCREASED RISK OF COMPLICATIONS
Older than 65 years without comorbidities
Under 65 with any of the following comorbidities:
• CSF leak, cochlear implant
Sickle cell anemia or other hemoglobinopathy
Anatomic or functional asplenia
Congenital immunosuppression or immunosuppression produced by an underlying disease such as HIV infection, chemotherapy or chronic corticosteroid treatment (> 2mg Kg/day of methylprednisone or its equivalent for > 14 days), hematopoietic cell transplant, solid organ transplant
Chronic renal failure/nephrotic syndrome
Leukemia or lymphoma
Hodgkin's disease
Widespread metastatic cancer
Iatrogenic immunosuppression including radiotherapy
Multiple myeloma
Smoker

Modified from [5] https://www.cdc.gov/flu/prevent/whoshouldvax.htm

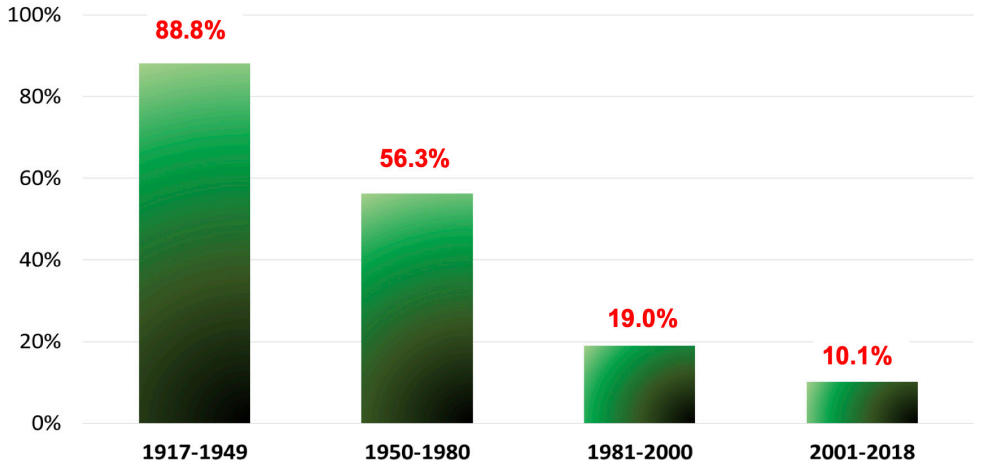

Figure 2 CDC estimate of influenza vaccine effectiveness for the 2004-05 through 2019-20 seasons. The 2020-21 season was not considered due to the low circulation of influenza observed during the pandemic. (Modified from:CDC seasonal Flu Vaccine Effectiveness Studies, 26 Aug, 2021 [6].

in which comparing the frequency with which vaccinated and unvaccinated get influenza or influenza-like illness. The results indicate that the vaccine has an impact on morbidity and mortality in immunized vs. non-immunized groups at risk. Such results are estimated annually by the CDC and if there is a low effectiveness in the observed result, this may be due to poor choice of target strain or to other reasons (Figure 1).

PNEUMOCOCCI

Streptococcus pneumoniae is the classic pathogen of CAP, its importance as a pathogen has been significantly reduced during the last century due to the convergence of the appearance of antibiotics in the middle of the last century and the high rates of vaccination for about 10 years from the development of conjugate vaccines in infants throughout the world, and secondarily from the vaccination of the rest of the population, particularly those over 60 years of age and people with comorbidities (Figure 2).

S. pneumoniae is a common respiratory pathogen that frequently causes "non-invasive" respiratory disease (otitis, sinusitis, pharyngitis, bronchitis, and CAP) and less frequently

invasive disease (bacteremia, severe CAP, empyema, meningitis, endocarditis, etc). The latter produces severe clinical pictures that may require intensive care and develop serious complications, including higher mortality.

In 1977 a pneumococcal vaccine was licensed that protected against 14 serotypes, in 1983 it was expanded to protect against 23 serotypes. This is a polysaccharide vaccine called PPSV23. It remained in force for more than 20 years since with penicillin and later the appearance of other antibiotics, the morbidity and mortality of this disease fell significantly (Alexander Fleming, discoverer of penicillin at the time, was encouraged to predict that the pneumonia would be the first infectious disease eradicated from the planet). Unfortunately, the PPSV23 vaccine was shown to be effective in preventing invasive pneumococcal disease, but the same did not occur with respect to non-invasive disease, and it did not work in children under 2 years of age. In 2000, a 7-serotype conjugate vaccine (PCV7) was licensed for infants. It drastically reduced mortality from invasive disease, especially meningitis. In the past decade, the 10-valent and 13-valent conjugate vaccines were approved, which improved its coverage in children and, a few years later, demonstrated their efficacy in reducing the incidence of invasive and non-invasive disease in those over 65 years of age, and from there began to be used especially in the elderly and people with comorbidities.

Currently, the 13-valent conjugate vaccine has been incorporated into the adult vaccination schedule. Given that the latest conjugate vaccine available (13-valent) has a coverage that is sufficient to cover approximately 50% of circulating serotypes, the use of sequential schemes of both types of vaccine, PPSV23-valent and PCV13, is recommended in adults, in a consistent manner to cover this situation. Table 3 shows the indications for the pneumococcal vaccine in adults.

The fact that PPSV23 is a polysaccharide vaccine has not shown with certainty its efficacy in preventing non-invasive forms of the disease [8]. Although different studies including a meta-analysis provided evidence that supports that PPSV23 would prevent invasive pneumococcal disease (IPD) in adults [9], non-invasive disease is not prevented by this vaccine, which is why the evidence is not clear regarding patients with chronic diseases. The vaccine is recommended in adults to prevent IPD [10].

In 2015, Bonten et al. published a double-blind, placebo-controlled, randomized study in which 84,496 subjects older than 65 years were randomly assigned to receive a single dose of PCV13 or placebo [11]. It was shown in the vaccinated subjects 45.6% fewer first episodes of CAP due to a serotype present in the vaccine compared to placebo ($p < 0.001$); 45.0% fewer episodes of non-bacteremic/non-invasive CAP due to a serotype present in the vaccine ($p = 0.007$) and 75.0% fewer first-episode IPD ($p < 0.001$). Throughout the world, national and continental scientific societies have developed guidelines for vaccination against pneumococcus for adults that contain both types of available vaccines. The Argentine Association of Respiratory Medicine designed a sequential scheme that is shown in figure 3 [12].

PERTUSSIS

Despite the existence of a vaccine to prevent it, whooping cough is a disease that is still present, mainly affecting young infants with high morbidity and mortality. But it also affects

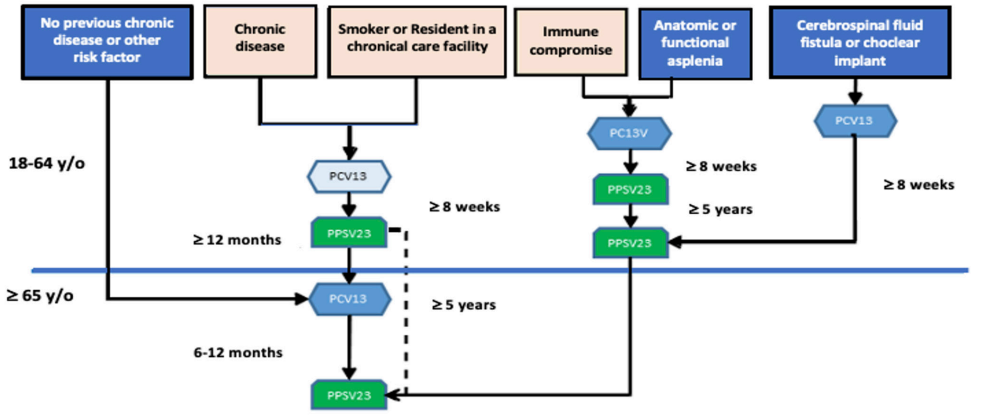

Figure 3 | **Pneumococcal vaccination schedule in adults [11]**

Includes immunodeficiencies (types T, B and Complement), HIV infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, malignant disease, transplant, iatrogenic immunosuppression (includes radiotherapy and corticosteroids)

Administering PCV13 to patients with chronic lung disease and/or smokers, older than 65 years, followed by the application of PPSV23 could provide better immunogenicity for vaccine serotypes in this age group.

adolescents and adults who have lost the effect of the initial vaccination; this second group has become the main reservoir and source of transmission of *Bordetella pertussis* to infants.

The new pertussis vaccines, formulated for this age group, have a good immunogenicity and safety profile and their efficacy reaches 92%. Currently, few countries have in their calendar the application of the acellular pertussis vaccine once in life in adults at the time of the application of the double bacterial vaccine (tetanus-diphtheria), replacing the latter in this case by the triple bacterial (tetanus-diphtheria-acellular pertussis).

The universal use of this vaccine could contribute to the control of whooping cough in the most susceptible groups. In those countries where this vaccine is not included in the schedule for adults, it is usually prescribed as an indication, at least in pregnant women between weeks 27 to 36 of their pregnancy and in health personnel, to reduce the potential contagion to infants [13].

SARS-COV-2

The appearance of the new coronavirus inaugurated a new era in vaccination against pneumonia-producing diseases. At the end of 2021, there are more than 10 widely distributed vaccines that have shown their efficacy and safety to control infection by the SARS-CoV-2 coronavirus, which have been developed in a very short time, so much so that they required urgent authorization for their use (Emergency Use Authorization, EUA), without having complied with the usual periods that regulatory agencies require for other vaccine developments. The platforms used have been messenger RNA: Moderna and Pfizer BioNTech; Viral vector (Adenovirus): AstraZeneca-Oxford, Janssen, Gamaleya and Cansino; Inactivated virus: Sinovac, Sinopharm Wuhan and Sinopharm Beiging.

Phase 3 randomized controlled clinical trials (RCCTs) reported an efficacy between 50 and 95% against symptomatic COVID-19, which enabled the use by the regulatory agencies (CDC, EMEA, etc) for vaccines that successfully passed phase 3 [14].

New studies may find differences in E with respect to RCCT (factors such as cold chain, interval between doses, circulating variants or incomplete vaccination).

Most of these vaccines were originally designed for 2 doses 3 to 12 weeks apart. The application of booster doses, initially to additional populations (e.g., children, pregnant women, the elderly, immunocompromised) and most likely extended to the rest of the population, became apparent after the appearance of new variants that began to show a loss of effectiveness, are approved based on their immunogenicity.

Further studies of efficacy will be necessary to confirm the inferences from the immunological data.

FUTURE DEVELOPMENTS

The future will be oriented in several objectives. About the flu vaccine, for many years the need to develop a "Universal" vaccine has been raised that is not aware of the viral "shift" or "drift" that forces us to be aware of the evolution of the virus to develop vaccines annually that require revaccination [13]. Regarding pneumococcus, the appearance of conjugate vaccines capable of preventing the development of invasive and non-invasive pneumococcal disease markedly changed the mortality attributable to this bacterium. However, this remarkable effect partially reduced its potential impact due to the appearance of serotypes absent in the PCV13 vaccine. This obstacle will be quickly resolved by the development of new vaccines such as PCV20, already approved by the FDA in the United States, which will possibly eliminate the need for sequential schemes [15,16]. As pointed out in the introduction, there are many viruses that are responsible for CAP in adults, which have not yet been considered. However, researchers are developing vaccines for other viruses, such as metapneumovirus and respiratory syncytial virus, which, although not yet available, they have posed problems of great magnitude, surely as pathogens or co-pathogens they are collaborating in morbidity and mortality, particularly in those over 60 years of age and in those with comorbidities, and in the future, we will also see new developments appear in this field.

CONFLICTS OF INTEREST

The author declares no conflicts of interest

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Pneumonia clinical reports

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Bacteremic pneumococcal pneumonia: arrhythmogenic disease

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Sir,

Streptococcus pneumoniae remains the most common cause of community-acquired pneumonia (CAP) [1]. Among pneumonia pathogens, it is the leading cause of hospitalization and death in adults [2]. Around 15-25% of cases of pneumococcal pneumonia (P-CAP) are bacteremic and these patients have worse in-hospital course and outcomes [3]. The development of cardiac complications in general and new- onset atrial fibrillation (AF) in particular has been documented in a substantial number of patients hospitalized for P-CAP and also associated with higher severity and in-hospital mortality [4].

We report a case of a 69-year-old male patient with well functional status, former smoker of 10 packs/year, not vaccinated against flu nor pneumococcus and with arterial hypertension in treatment with valsartan/hydrocholothiazide. He attended emergency department whit a 2-day history of cough with purulent sputum, fever up to 39ºC and breathlessness. On physical examination, he presented hypotension of 89/58, tachycardia of 127bpm, fever of 37.8ºC, O_2 saturation of 89% and respiratory rate of 32bpm. On pulmonary auscultation he presented right crackles. In the serum chemistry he had a creatinine of 1.8mg/dL, C-reactive protein (CRP) of 373mg/l and procalcitonin of 9.05ng/ml. In the hematimetry he had 4100 leukocytes/µL (80% neutrophils) and the prothrombin index was 39%. In arterial blood gas, the partial pressure of oxygen (pO_2) was 56mmHg. Chest X-ray showed a right upper lobe consolidation. Blood cultures were performed, and urinary antigen rapid test was positive for *S. pneumoniae*. In the electrocardiogram a rapid AF was observed. Pneumonia Severity Index (PSI) [5] was used to assess severity and prognosis of the pneumonia. The score of the patient was 159 points, indicating class V (high risk). The 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia [6] were also applied, observing that the patient met 3 minor criteria. Considering the result of the severity scales together with clinical judgment, the patient was admitted to the intensive care unit (ICU). He was empirically treated with azithromycin 500mg + ceftriaxone 2g daily according to the recommendations of current guidelines of Spanish Society of Pulmonology [SEPAR] [7]. As the patient had a hypoxemic respiratory failure he was treated with high-flow oxygen therapy. The septic shock did not respond to fluid replacement and the patient needed treatment with vasopressors to restore perfusion and recover renal function. The rapid AF was treated with amiodarone and anticoagulation according to the result of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category) of high risk of stroke. After few days of hospital admission, the blood culture result was positive for *S. pneumoniae*, serotype 3. Once clinical and haemodinamic stability was achieved and with the result of the blood culture the antibiotic treatment was de-escalated to ceftriaxone. The in-hospital evolution of the patient was satisfactory; 5 days after admission the high flow oxygen therapy was withdrawn, and the patient was transferred to ward. He was discharged 13th day after admission presenting permanent AF.

S. pneumoniae is the most identified pathogen in pneumonia. Despite the prognosis of P-CAP has improved in recent years due to new vaccines, early diagnosis, and improvements in treatment, it usually causes severe CAP, being responsible for the highest rates of bacteremia, hospital admission and mortality. Bacteremic P-CAP has traditionally been considered an invasive form of infection and previous studies have related it to higher inflammatory status, worse in-hospital course and shorter long-term survival [3].

Organism-related factors play a key role in the clinical

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course of the disease. The capsular polysaccharide is probably the major virulence determinant of *S. pneumoniae*, protecting it from phagocytosis. At present, 100 pneumococcal serotypes have been described based on differences in the antigenic characteristics of capsular polysaccharides. Previous studies have shown that pneumococcal serotypes differ in properties such as resistance to phagocytosis, ability to penetrate into tissues and capacity to activate the inflammatory response and this translates into differences in the severity of the illness and mortality depending on the pneumococcal serotype. Serotype 3 is the most frequent, it has low invasive potential, affecting older patients with comorbidities and it is a high-risk serotype causing higher case-fatality rate. P-CAP caused by serotype 3 is independent risk factor for respiratory failure, bilateral involvement upon radiography, need for mechanical ventilation or septic shock [8]. Sanz et al. [9], developed a prospective, multicenter study of 463 patients with bacteremic P-CAP and high inflammatory level defined for CRP> 15 mg/dl, in which 97 patients (21%) were infected with serotype 3. Patients with P-CAP caused by serotype 3 showed significantly more septic shock, ICU admission, respiratory, systemic, and cardiovascular complications compared to other serotypes.

One important aspect of severe CAP that contributes to worse in-hospital course and mortality are major adverse cardiovascular events. Up to 30% of patients admitted to hospitals with invasive pneumococcal disease experience cardiac complications and new or worsening arrhythmia is the most frequent one. Moreover, pneumococcal bacteremia has been identified to be an independent risk factor for acute cardiovascular events. The elevated inflammatory response in patients with bacteremia is directly associated with its development. The presence of cardiac lesions during the acute invasive pneumococcal infection together with the production of pneumolysin seems to be involved in the genesis of this type of complications. Ruiz et al. [4], in a previous study of our group in a cohort of 1,092 patients with P-CAP, of whom 109 (9.9%) had new-onset AF, have been able to correlate the development of early new-onset AF to bacteremia and severe inflammation. We have observed a progressive increase in AF onset with PSI risk class. Patients who developed new-onset AF had a significantly more prolonged hospital stay, and higher rate of ICU admission and in-hospital mortality. In the same way, failure to restore sinus rhythm was associated with increased in -hospital mortality and lower 6- month survival rate.

After analyzing the severity and risk of short- and long-term complications after bacteremic P-CAP it is clear that we need to make efforts to protect against *S. pneumoniae,* and the best preventive method is vaccination. Nowadays there are two vaccines available against pneumococcus: Pneumococcal Conjugate Vaccine or PCV13 and Pneumococcal Polysaccharide Vaccine or PPSV23. PCV13 has shown higher efficacy and longer duration than PPSV23 in immunocompetent subjects with risk for vaccine serotypes in non-bacteremic CAP, thus as in the bacteremic P-CAP. Risk factors include heart disease, chronic liver, kidney and respiratory diseases (includes asthma), cancer, diabetes, chronic alcoholism, smoking, transplantation of solid organ or hematopoietic cells, cochlear implants, cerebrospinal fluid fistula, anatomical or functional asplenia and antecedent of bacteremic P-CAP.

In conclusion, bacteremic P-CAP is associated with high severity and worse in hospital course. Serotype 3 is the most frequent and is related to septic shock and respiratory failure. The development of acute cardiovascular events, especially new-onset AF is associated with pneumonia severity, and higher in-hospital and short term mortality. Bacteremia and severe systemic inflammation are factors associated with its development. It is necessary to make efforts to widen pneumococcal vaccination coverage especially in aged patients and/or those with chronic comorbid conditions.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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Pneumonia clinical reports

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Pulmonary Nocardiosis. A case report

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Sir,

Chronic obstructive pulmonary disease (COPD) is a chronic disease which predisposes to the appearance of opportunistic infections. Long-term corticosteroids therapy might favor this immunosuppression status. Next, we report a case of a COPD patient with a non-responding pneumonia, in which immunosuppression was potentiated by previous corticosteroid treatments and mucociliary clearance alteration.

A 75-year-old caucasian male, ex-smoker, with a medical history significant for type I obesity and severe COPD disease treated with triple bronchodilator therapy, presented at Emergency Department (ED) with dyspnea, cough and expectoration from 1 week. A blood sample analysis revealed high acute-phase reactants (leucocytosis [21,900 cells/µL], neutrophilia [21,150 cells/µL], and high C-reactive protein (CRP) [173.6 mg/L]), with normal kidney function and haemostasis. Chest-X-ray showed no new infiltrates or consolidation images. After ED medical treatment, the patient improved and was discharged with oral treatment (cefditoren and prednisone).

At home, the patient was clinically worsening and two months later he presented again at ED with pleuritic chest pain, dyspnea and tachypnoea (respiratory rate: 30 breaths per minute). New complementary explorations were completed: Blood analysis revealed high acute-phase reactants (leucocytosis [22,430 cells/µL], neutrophilia [18,810 cells/µL], high CRP [91.6 mg/L]) and a right lower lobe consolidation with ipsilateral pleural effusion was shown in chest-X-ray (Figure 1). Arterial blood gas showed moderate hypoxemia despite supplemental oxygen therapy (FiO2 0.35). Hence, he was hospitalized with the diagnosis of community-acquired pneumonia.

Initially, symptoms improved after endovenous levofloxacin, methylprednisolone treatment and bronchodilators. The microbiological tests (atypical bacteria serology, urine antigens for legionella and pneumococcus, and respiratory viruses) were all negative and sputum was cultured. Seventy-two hours after admission, symptoms, blood sample analysis and oxygenation parameters worsened. Chest ultrasound showed little quantity of pleural effusion not subsidiary to thoracentesis. Sputum culture was positive for *Aspergillus fumigatus*. As considered a treatment failure, antimicrobial coverage was broadened (piperacillin/tazobactam and oral voriconazole) and a CT-scan and a bronchoscopy were requested for obtaining invasive samples.

The CT-scan showed bilateral pulmonary nodules, with many lobes involved, heterogeneous in size (4-36mm) with hypodense regions of probable necrosis. The right basal consolidation has progressed and the pleural effusion persisted (Figure 2). A bronchoscopy was performed and it revealed abundant mucopurulent secretions. A bronchoalveolar lavage (BAL) was obtained from lingula.

The BAL microbiological tests showed negative results for respiratory viruses, fungi culture, galactomannan antigen and mycobacterial tests (Ziehl-Neelsen stain and Lowenstein culture). A *Nocardia cyriacigeorgica* grew in culture and antibiotic susceptibility was performed.

Because of the moderate-grade pulmonary nocardiosis, intravenous cotrimoxazole was started (sensitivity was confirmed). The patient showed clinical improvement, then intravenous antibiotic therapy was switched to oral cotrimoxazole. After 6 months of treatment, chest X-ray showed disappearance of consolidation, the patient was asymptomatic with no adverse reactions to treatment and treatment was discontinued.

Pulmonary nocardiosis (PN) is an opportunistic infection that belongs to *Actinomycetaceae* family and mainly affects immunocompromised patients. However, in one third of cases it can occur in immunocompetent patients. *Nocardia spp.* are Gram-positive, aerobic, filamentous, and partially acid-fast bacilli. PN has a high mortality rate up to 38% according to some case series [1].

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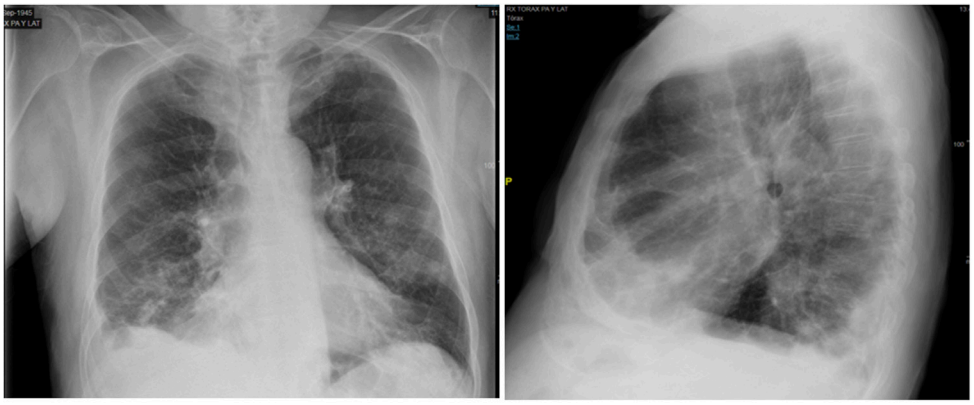

Figure 1 | **Chest-X-ray. Right lower lobe consolidation with ipsilateral pleural effusion.**

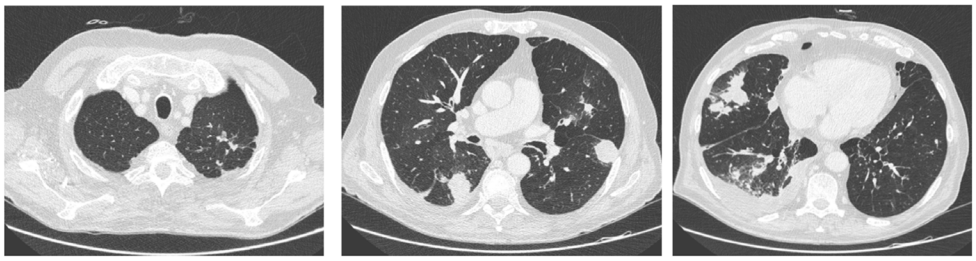

Figure 2 | **CT-scan. Bilateral pulmonary nodules with hypodense regions. Progression of the right lower lobe consolidation. Pleural effusion.**

Nocardiosis incidence is increasing due to the greater longevity of population, which has a senescent immune system [2] and higher number of chronic advanced comorbidities. Local alteration of the pulmonary defences predisposes to PN, as it occurs in COPD or lung sequestration [3,4].

Direct inoculation or inhalation of spores are the main transmission mechanisms of *Nocardia*. They may be found in sand, dust or in stagnant water [3].

Lung involvement is the main affectation of *Nocardia*. However, disseminated involvement may occur in some cases (≥2 sites involvement in 32% of patients, according to case series). Disseminated disease involves central nervous system, bacteraemia and cutaneous or soft tissue infections [5].

Differential diagnosis of PN should be made with other infectious and non-infectious diseases, such as pneumocystis pneumonia, tuberculosis, fungal infections or ANCA-mediated vasculitis [2].

Gold standard for the identification of PN is the culture of *Nocardia*. *Nocardia* is a slow-growing bacterium that requires specific stains (Kiyoun or fluorescent auramine-rhodamine) and special cultures (modified Thayer Martin agar or BCYE-alpha agar). In other non-selective media, such as media for Mycobacteria, it can also grow (Löwenstein-Jensen) [5]. Molecular identification methods, such as Polymerase Chain Reaction (PCR) base sequencing, provide rapid results. However, these techniques are not available in all microbiology laboratories [2].

In immunosuppressed patients, a positive sputum culture leads to diagnosis of the disease and not only colonization [3]. In 44% of lung infections, invasive diagnostic procedures for obtaining lower respiratory samples may be necessary [6].

Decontamination methods (sodium hydroxide, benzalkonium chloride and N-acetyl-L-cysteine) are toxic for *Nocardia* [2] therefore, it is essential to inform to the microbiology laboratory if there is clinical suspicion.

Standard treatment for local PN is cotrimoxazole. Initially, intravenous administration is recommended. If clinical improvement is achieved, an oral administration could be considered. The treatment total duration is 6 months, although it must be extended to 12 months in immunosuppressed patients or in disseminated disease. In severe lung diseases or immunosuppression, combined treatment (cotrimoxazole + amikacin or imipenem + amikacin) is recommended. In associated central nervous system involvement, triple therapy with cotrimoxazole + imipenem + amikacin is recommended [7].

In conclusion, PN should be considered in immunosuppressed patients and, also in patients with other associated risk factors. Clinical suspicion is very important because specific microbiological tests are required. Nocardiosis requires prolonged and sometimes combined treatment.

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Pneumonia clinical reports

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Recurrent ventilator-associated pneumonia caused by "difficult to treat" resistance *Pseudomonas aeruginosa*

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Sir,

We hereby present a clinical report with three key points. Firstly, ventilator-associated pneumonia is the most frequent nosocomial infection in Intensive Care Units (ICU). Second, *Pseudomonas aeruginosa* is currently the most frequently isolated causative microorganism in Spanish ICUs. And third, this non-fermenting gram-negative bacillus has multiple virulence mechanisms that enable colonization and subsequent tissue invasion. It also has the ability to form biofilms that facilitate its persistence and therefore, infection recurrence. Likewise, it is characterized by a remarkable intrinsic resistance, along with an extraordinary capacity to acquire resistance to practically all available antibiotics, including the new β-lactams with β-lactamase inhibitors (BL/BLI), such as ceftazidime–avibactam, as we describe in the following case report.

A 62-year-old male patient with the following medical history: arterial hypertension, dilated heart disease of ischemic origin with severe left ventricular dysfunction, and chronic hepatitis B infection. The patient had a left colostomy carrier after a complicated acute diverticulitis. He was admitted to the hospital with the diagnosis of bilateral SARS-CoV-2 pneumonia, 3 weeks after the onset of symptoms. Pulmonary CT was compatible with severe bilateral SARS-CoV-2 lung infection (CO-RADS 6) (Figure 1). He remained in the respiratory care unit for 20 days, requiring high-flow oxygen therapy. He received treatment with dexamethasone (initial dose 6 mg/day) along with ceftriaxone and piperacillin-tazobactam as empirical antibiotic treatment for suspected coinfection. He was admitted to the ICU and required intubation, mechanical ventilation and two prone position sessions due to severe acute respiratory distress syndrome (ARDS) with PaO_2/FiO_2 <100mmHg. APACHE II: 11 points. SOFA score: 9 points.

On day 11 upon admission to the ICU, he met clinical, radiological and microbiological criteria for nosocomial pneumonia. Empirical therapy was initiated using meropenem and linezolid. *P. aeruginosa* (AmpC profile) was isolated in a tracheobronchial aspirate (meropenem MIC 1 mg/L). Antibiotic treatment was adjusted and the patient continued receiving meropenem for 10 days. On day 36, the patient developed a new episode of nosocomial pneumonia complicated by secondary bacteremia. Carbapenem-resistant *P. aeruginosa* (meropenem MIC > 16 mg/L) was isolated. Initial empirical treatment with meropenem and colistin was adjusted to ceftazidime-avibactam for 14 days based on *in vitro* susceptibility test results. Finally, on day 78 upon admission to the ICU, whilst on weaning, the patient presented tracheobronchitis due to extensively drug-resistant *P. aeruginosa*, which included ceftazidime-avibactam resistance (MIC 32 mg/L). The isolate showed optimal in vitro activity to ceftazolane-tazobactam, colistin, and tobramycin. The patient was treated with ceftalozane-tazobactam and inhaled colistin.

Prolonged mechanical ventilation, the need for a tracheostomy, and multiple weaning attempts determined the evo-

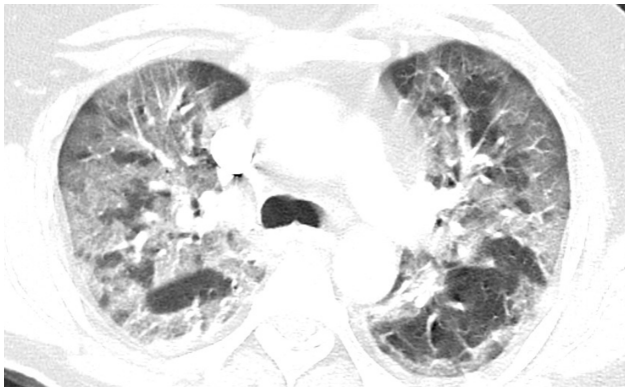

Figure 1 CT: Highly suggestive of severe bilateral SARS-CoV-2 lung infection.

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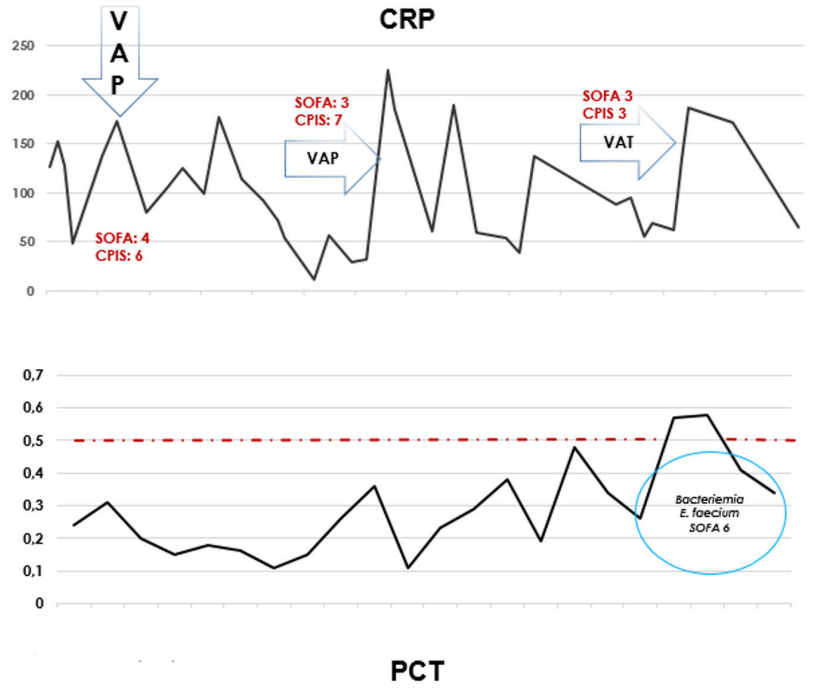

Figure 2 | **Biomarker evolution: C-reactive protein (CRP mg/L) and procalcitonin (PCT ng/dl). Sepsis-related Organ Failure Assessment (SOFA) and Clinical Pulmonary Infection Score (CPIS). VAP: Ventilator-associated Pneumonia. VAT: Ventilator-associated Tracheobronquitis.**

lution and ICU length of stay of the patient. During his admission, *Aspergillus fumigatus* was isolated from a respiratory tract sample, which would be treated according to clinical severity criteria. The patient also develops two bacteremias due to *Enterococcus faecium*, and many other febrile episodes for which he received multiple antibiotics.

The evolution of biomarkers throughout the admission is shown below. In our case, CRP kinetics adjusted better to the different infectious episodes compared to procalcitonin, which would only got over 0.5 ng/ml in the course of enterococcal bacteremia. CPIS and SOFA score values are displayed. (Figure 2) A few days after the episode of tracheobronchitis, the patient was discharged from ICU and later transferred to a rehabilitation healthcare center.

In the 2020 ENVIN-HELICS study, 17.3% of patients included developed a nosocomial infection, the most frequent being ventilator-associated pneumonia (VAP) (36.8%). Overall mortality was 44%. *P. aeruginosa* was the most frequently isolated microorganism (22.9%). Resistance to ceftazidime, cefepime, and piperacillin-tazobactam was 35% and imipenem 42% [1].

Risk factors associated with VAP caused by *P. aeruginosa* include older age, diabetes, immunocompromised status, cystic fibrosis, chronic obstructive pulmonary disease, prolonged hospital and ICU stay, presence of tracheostomy, extended ventilation periods, recent surgery, and high baseline severity. Previous antibiotic exposure to anti-pseudomonal beta-lactams, quinolones, and aminoglycosides favours the acquisition of multidrug-resistant strains [2].

P. aeruginosa's pathogenicity is very complex. This pathogen uses a series of functional elements, to move and adhere on living and nonliving surfaces, such as different tissues and medical devices. In addition, *P. aeruginosa* forms bacterial communities with a complex intercelular communication mechanism, surrounded by a polisaccharides-based structure known as biofilm. This structure acts as a barrier, providing a favorable environment for colony survival, and playing and important role in the chronic colonization or infection process [3].

Literature suggests that up to 17% of patients with *P. aeruginosa* bacteremia will have a recurrent infection, frequently associated with the severity of comorbid conditions and a concomitant increase of mortality rates [4]. Recurrent episodes of VAP cause by *P. aeruginosa* occur due to persistence of strains present in a prior infection. Previous studies have shown a considerable disparity in the incidence of this complication (3-50%), most frequently in patients with ARDS [5]. VAP incidence rates among COVID-19 ARDS patients are much higher than pre-pandemic rates in non-Covid patients, and a higher rate of recurrence VAP episodes has been ob-

served (up to four events in a single patient) even in patients with appropriate antimicrobial treatment [6].

"Difficult-to-treat" resistance is defined as *P. aeruginosa* that exhibits non-susceptibility to all of the following antibiotics: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastin, ciprofloxacin, and levofloxacin. Ceftalozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam are first-line options, assuming in vitro susceptibility for infections outside of the urinary tract, and cefiderocol could be an alternative treatment if first-line antibiotics are not available or tolerated [7].

Resistance induction by ceftazidime–avibactam remains an issue of concern, with diminished outer membrane permeability and overexpression of efflux pumps or AmpC as underlying mechanisms. Whilst some studies have reported resistance ceftazidime–avibactam rates of 20%, resistance was not detected in other series [8]. Although AmpC derepression also increases MIC of ceftalozane-tazobactam, clinical resistance to this new combination requires an additional structural modification of AmpC, which could explain the lower development of resistance. Furthermore, in those infections linked to high bacterial load, the probability of resistance development is elevated for most classical antipseudomonials. This is because mutant prevention concentrations are frequently above those achieved by systemic administration, except for colistin and ceftalozane-tazobactam [9]. This is perhaps, an advantage to be taken into account in *P. aeruginosa* VAP treatment.

The increasing prevalence of multidrug-resistant strains is a cause of concern as it compromises the selection of appropriate empirical and definitive antimicrobial treatments. This situation is associated with worse outcomes and higher mortality, mostly in patients with severe infections, as bacteremia and ventilator-associated pneumonia [10]. Empirical antibiotic treatment against *P. aeruginosa* should be initiated taken into account prior antibiotic therapy, local epidemiology and susceptibility of previous isolates.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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Pneumonia clinical reports

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Mechanical ventilation associated pneumonia during ECMO therapy. A challenge for the Intensive Care physician

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Sir,

We present the clinical case of a young patient who suffered from SARS-CoV-2 pneumonia, which required veno-venous ECMO, and was complicated by fatal nosocomial pneumonia associated with mechanical ventilation.

This is a 33-year-old patient with a history of systemic erythematosus lupus (SEL) and bronchial asthma, for which she was receiving home treatment with prednisone, colchicine, beclomethasone-formoterol, and salbutamol. At that time, not vaccinated against SARS-CoV-2.

The patient had a non-productive cough, dyspnea and fever, so a week after the onset of the symptoms, a PCR for SARS-CoV-2 was determined, which resulted positive. After a torpid evolution at home, one week later (14 days from the start of the symptoms) she was admitted to the Internal Medicine hospitalization ward of her reference hospital. Upon admission, treatment was started: remdesivir (for 10 days), dexamethasone (8 mg for 5 days and 20 mg for a further 5 days), tozilizumab (2 doses of 600 mg), as well as empirical antibiotic therapy with ceftriaxone and azithromycin (hours after the admission, the *S. pneumoniae* and *L. pneumophila* antigenuria were negative, so the aforementioned treatment was interrupted). In addition, intermediate doses of enoxaparin (1 mg/kg/day) and oxygen therapy in nasal cannulas were prescribed. After 4 days of hospital stay, and despite the measures, she presented further clinical deterioration, requiring high-flow nasal oxygen therapy, which is why she was admitted to the Intensive Care Unit (ICU) of the aforementioned hospital. The patient worsened and did not tolerate non-invasive mechanical ventilation, and after 4 days of stay in the ICU, intubation and invasive mechanical ventilation were performed. Despite ventilation, the situation of refractory hypoxemia persisted, even to prone maneuvers and lung recruitment. With a pO2/fiO2 ratio of 72 mmHg on the third day of invasive ventilation, we were consulted and the ECMO team from our hospital was moved to establish femoro-femoral veno-venous extracorporeal therapy (cardiac function resulted normal by echocardiography). After that, she was transferred by medicalized ambulance to our hospital (distance: 206 km). During the days after the extracorporeal circulation was initiated, protective lung ventilation was possible, maintaining a control pressure of 15 cmH2O, PEEP of 10 mmHg, respiratory rate between 10-12 breaths/min, and FiO2 of 60%. The chest X-ray showed a bilateral alveolar and interstitial pattern with bibasal pleural effusion (virtually a "bilateral white lung").

On the fifth day of ECMO care, the patient presented a low-grade fever of 37.7ºC (the extracorporeal device had a temperature control system incorporated), which was accompanied by a rise in the biomarkers (procalcitonin from 0.05 to 1.4 ng/ml and C-reactive protein: from 9 to 74 mg/l), leukocytosis with neutrophilia as well as increased quantity and purulence of respiratory secretions. Chest ultrasound revealed a consolidated lung parenchyma from upper to lower fields, with subpleural nodules and bilateral pleural effusion. Two diagnostic and therapeutic thoracocentesis were performed (no empyema), microbiological cultures were performed and meropenem and linezolid were empirically added due to the suspicion of mechanical ventilation associated pneumonia. Both the respiratory sample and the blood cultures grew *Pseudomonas aeruginosa*, vulnerable to ceftolozane/tazobactam and ceftazidime/avibactam, as well as to aminoglycosides and colistin, being resistant to meropenem. Antibiotic therapy was adjusted: meropenem was suspended and ceftazidime/avibactam was added (ceftolozane/tazobactam was not available).

After a few days of clinical stability, marked by dependence on extracorporeal support for oxygenation, a radiological improvement being able to maintain the range of ventilatory pressures at 15 cmH2O and without requiring vasoactive/inotropic drugs to maintain adequate blood pressure, on day 19 of Extracorporeal assistance the patient presented a se-

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rious deterioration of the ventilatory function, which forced to increase the blood flow by ECMO (75-80% of the patient's cardiac output), to carry out ventilation in prone position (up to 5 cycles) as well as to start nitric oxide therapy (up to 20 ppm). At that time, the Herpes virus type 1 was detected in the respiratory secretions (not fungi), and in both respiratory secretions and blood cultures, the sensitivity pattern of Pseudomonas aeruginosa (which continued to grow significantly) changed: it became vulnerable only to colistin, tobramycin, aztreonam-avibactam and cefiderocol. After directed antibacterial adjustment (intravenous and inhaled in a different combination of antibiotics with demonstrated sensitivity), on day 34 of ECMO care the patient progressed to a situation of septic shock of respiratory origin that required starting, in addition to vasoactive drugs at maximum doses, continuous venovenous hemodiafiltration at high flow (coupled to ECMO). Despite the extracorporeal oxygenation therapy and the adjustments in mechanical ventilation, dynamic compliance was less than 10 mL/cmH2O at all times and the pO2/fiO2 ratio was only 50-75 mmHg. Echocardiography revealed a hyperdynamic pattern at that time, and chest X-ray revealed pulmonary cavities in the upper lobes and middle lobe with complete consolidation of the rest of the lung parenchyma. Nevertheless, three days later the hemodynamic situation improved, the dose of vasopressors could be reduced, peripheral perfusion returned to normal status (lactate in the normal range) with no signs of ventricular dysfunction by echocardiography. However, severe respiratory dysfunction persisted, with extreme difficulty in ventilation performing (tidal volumes less than 100 ml). Despite to optimizing PEEP, performing cleaning fiberoptic bronchoscopy and attending the 90% of cardiac output by extracorporeal oxygenation, the pO2/fiO2 was only 50 mmHg (dynamic compliance 4 ml/cmH2O). In this situation, the patient was transferred to Radiology department and a chest CT scan was performed (Figure 1): it showed pulmonary cavities, which were large in both upper lobes (11 cm in the left) and in the middle lobe, with air-fluid levels, probably due to necrosis of the parenchyma and communication with the airway (less probably pneumatoceles). In addition, multiple small bilateral cystic lesions were identified, which could correspond to pneumatoceles or bronchial cystic dilatations, with complete consolidation of the pulmonary parenchyma.

On the 39th day of care, hemodynamic instability occurred again and the echocardiography showed an acute dilatation of the right ventricle, in addition to severe tricuspid regurgitation, whose gradient allowed estimating a systolic pulmonary arterial pressure of 80 mmHg. In this scenario of claudication of the right ventricle and refractory hypoxemia, it was decided to change the configuration to veno-arterial (femoro-axillary) ECMO, but despite the measures, multi-organ failure occurred and finally the patient death after 42 days of ECMO support.

In the current pandemic context, the main international organizations, including the World Health Organization, the Surviving Sepsis Campaign or the Extracorporeal Life Support Organization (ELSO), recommend the use of ECMO therapy in acute respiratory distress syndrome (ARDS) associated with

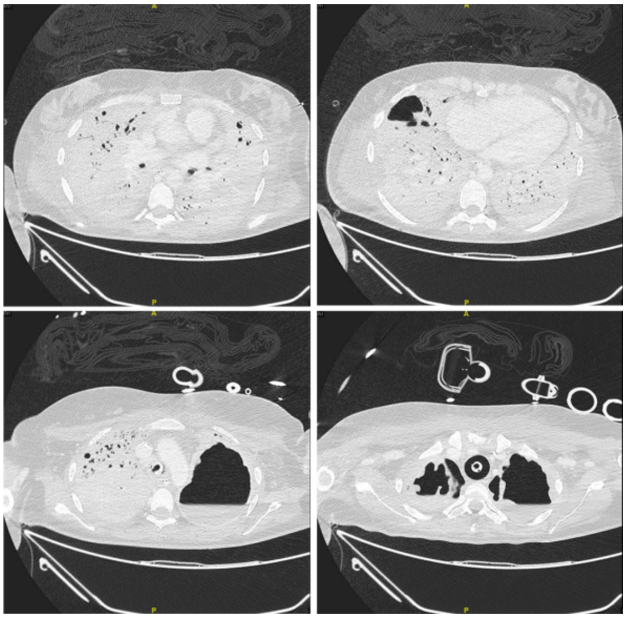

Figure 1 | **Chest CT scan**

COVID-19 presenting with hypoxemia refractory to conventional mechanical ventilation. The rate of ECMO use during the pandemic ranges from 0.5-1% of all hospitalized patients.

But ECMO therapy is not without risks, with nosocomial infections being one of the most frequent complications. These infections are described in up to 64% of patients undergoing this technique, with rates of 30.6 infectious episodes per thousand days of device use according to the ELSO prevalence study [1]. The factors that are directly related to the development of infection during ECMO therapy are adult age, the severity of the underlying disease, immunosuppression, the duration of ECMO support (from the second week of assistance, the chances of developing any infection exceed 50%), the ICU stay duration, as well as the support modality (in adults, veno-arterial therapy). The development of these infections is associated with increased mortality [2,3].

Primary bacteremias are the most frequently described infections during the extracorporeal therapy. But other infections associated with invasive devices, such as catheter-associated urinary tract infection and mechanical ventilation associated pneumonia (VAP) also have an increased incidence (the latter, in our environment, around 15 episodes per thousand mechanical ventilation days) [4].

However, diagnosing nosocomial infection in patients undergoing ECMO can be challenging. The blood exposure to the oxygenating membrane can provoke a systemic inflammatory response even in the absence of infection, a factor that in turn limits the validity of biomarkers such as procalcitonin and C-reactive protein for the infection diagnosis. The heat-cold exchanger used to regulate the body temperature interferes

with the detection of the febrile response to infection. In addition, it is the extracorporeal membrane itself that will ensure the oxygenation (and decarboxylation) of the blood, factor that can mask the impact of the infection on gas exchange in the lungs. All this can make the clinical diagnosis of VAP difficult, and also makes that some predictive scores of prognosis and evolution, such as the Clinical Pulmonary Infection Score (CPIS) [5], have a limited accuracy in this context.

In the case of our immunosuppressed patient, after having undergone conventional mechanical ventilation and ventilation in the prone position, she required connection to ECMO due to prolonged refractory hypoxemia, which prolonged her ICU stay, all of them factors that favored the appearance of several episodes of nosocomial infection, including VAP. In this case, the clinical and radiological diagnosis was microbiologically confirmed.

Despite specific antibacterial combinations, the patient developed a refractory septic shock caused of multidrug-resistant *P. aeruginosa*. The aggressiveness of the infection could be documented in the radiographic series and in the chest CT scan, which showed lung parenchyma cavitation, a factor that made it difficult to control the infection source.

Unfortunately, our case confirms the already published findings that patients with SEL who suffer from ARDS in the context of SARS-CoV-2 virus infection have a higher risk of mortality compared to patients without lupus disease. This risk is also higher than that of other morbidities such as arterial hypertension, diabetes mellitus, solid organ transplantation, smoking, alcoholism, obesity, solid neoplasms, and chronic heart, kidney, lung, or liver diseases, which all are also predisposing factors for increased mortality in the ARDS associated to SARS-CoV-2 infection [6].

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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