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Review

Towards a holistic approach to pulmonary infections. Insights from the Sixth Annual Meeting of Spanish Experts 2024

Hacia un abordaje integral de las infecciones pulmonares. Claves desde la Sexta Reunión Anual de Expertos Españoles de 2024

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Abstract

Pneumonia is the leading cause of death from infection in the developed world. In recent years, researchers and healthcare professionals have worked extensively to reduce this burden. Prevention is better than cure, and significant advances have been made in areas such as vaccination and the prevention of nosocomial pneumonia in intensive care units. Comprehensive surveillance programmes and new diagnostic methods have been developed to assess trends in this disease and to identify the infectious agents involved. Clinical presentation can be challenging in elderly patients or those with certain comorbidities, prompting new studies in these populations to address these issues. Correct and early management of severe community-acquired pneumonia represents a major opportunity to reduce its associated mortality. Although fungal pathogens are an uncommon cause of lung infection, they are associated with high morbidity and mortality, highlighting the need for new approaches. Finally, new drugs are available for the treatment of pneumonia, and a thorough understanding of them is key to ensuring their correct use, particularly to combat multi-resistance. To provide an update on these points, a multidisciplinary team of Spanish experts convened at the Sixth Annual Meeting of Pneumonia Day, under the scientific sponsorship of GEIPC-SEIMC. This paper reflects the information shared at this meeting, offering the latest insights on these topics and supporting a holistic approach to pneumonia management.

Keywords: Community acquired pneumonia. Aetiology. Management. Therapeutic failure. Nosocomial pneumonia. Healthcare-associated pneumonia. Epidemiology. Diagnosis stewardship. Prevention.

Resumen

La neumonía es la principal causa de muerte por infección en el mundo desarrollado. En los últimos años, investigadores y profesionales de la salud han trabajado intensamente para reducir esta carga. Más vale prevenir que curar, así que se han invertido importantes esfuerzos en ámbitos como la vacunación y la prevención de la neumonía nosocomial en las unidades de cuidados intensivos. Se han desarrollado programas de vigilancia integral y nuevos métodos de diagnóstico para evaluar las tendencias de esta enfermedad e identificar los agentes infecciosos implicados. La presentación clínica puede ser desafiante en pacientes de edad avanzada o con ciertas comorbilidades, lo que ha impulsado la realización de nuevos estudios en estas poblaciones para abordar estos problemas. El tratamiento correcto y precoz de la neumonía adquirida en la comunidad grave representa una gran oportunidad para reducir su mortalidad asociada. Aunque los hongos son una causa infrecuente de infección pulmonar, se asocian a una elevada morbilidad y mortalidad, lo que resalta la necesidad de nuevos enfoques diagnósticos y terapéuticos. Por último, se dispone de nuevos fármacos para el tratamiento de la neumonía, y un buen conocimiento de estos es la clave para su correcta utilización, especialmente para combatir la multirresistencia. Para actualizar estos temas, un equipo multidisciplinar de expertos españoles se reunió en la VI Jornada Anual de Neumonía, bajo el auspicio científico del GEIPC-SEIMC. Este documento refleja la información compartida en esta reunión, en la que se presentan los últimos avances sobre estos temas y se ofrece información relevante para un abordaje integral de la neumonía.

Palabras clave: Neumonía adquirida en la comunidad. Etiología. Manejo. Fracaso terapéutico. Neumonía nosocomial. Neumonía asociada a la asistencia sanitaria. Epidemiología. Diagnóstico. Prevención.

Introduction

Pulmonary infections are a major cause of death and morbidity worldwide. Community-acquired pneumonia (CAP) is the infection disease with the highest mortality in industrialised countries [1]. Hospital-acquired pneumonia (HAP) is defined as a pulmonary inflammatory and infectious process that begins more than 48 hours after hospital admission and was not present or incubating on admission. Ventilator-associated pneumonia (VAP) is a significant subset of HAP that occurs in patients with an artificial airway after 2-3 days of tracheal intubation [2–4]. Both entities are an important source of morbidity, disability, healthcare costs, and mortality [5–9].

In recent years, great efforts have been made to combat this disease, from prevention to the use of new therapies to reduce the damage it causes. There are many and varied preventive measures. Improvements in vaccination of children and adults in the community have been made in recent years, and new therapies are emerging to decontaminate the digestive tract to prevent VAP in the intensive care unit (ICU). Surveillance programmes have also improved, and interesting information is now available. The diagnostic process can be challenging in certain types of patients, such as those with immunosuppression, cancer, and advanced age. A correct approach to severe CAP is key to achieving better clinical outcomes. Although uncommon aetiological agents such as fungi are associated with worse outcomes, partly due to late diagnosis, so better management is needed. Finally, in the last fifteen years, new antibiotics and beta-lactamase inhibitors have become available to treat our patients. Therefore, considering this vast and diverse amount of information, we will only be able to help our patients with pneumonia from a multidisciplinary perspective.

Since 2019, Spain has hosted an annual meeting bringing together major medical societies involved in the diagnosis and treatment of pneumonia. The sixth meeting was held on 11-12 November 2024 [10]. Experts from different medical specialties involved in its management presented the latest advances in their respective fields and addressed the questions raised in the previous paragraph. This article aims to summarise the key ideas from each presentation given during the meeting, in relation to the scientific programme.

Material and methods

Design

The Study Group on Infection in Critically Ill Patients of the Spanish Society of Infectious Diseases and Clinical Microbiology (GEIPC-SEIMC) invited experts from various Spanish Medical Societies (listed in the affiliations of this document) involved in the diagnosis, treatment and prevention of CAP, HAP, and VAP caused by common and emerging pathogens, in different types of immunocompetent hosts (with or without comorbidities) and immunosuppressed (neoplastic, neutropenic, transplanted), to make a narrative review of their respective field of knowledge and to present their conclusions in different workshops at the Annual Meeting on Pneumonia.

Search strategy

Between July and November 2024, the experts performed a bibliographic search of their corresponding topics in PubMed ((http://www.ncbi.nlm.nih.gov/pubmed/, accessed on 1 November 2024), Embase (http://www.elsevier.com/online-tools/embase/, accessed on 1 November 2024) and Scopus (http://www.elsevier.com/onlinetools/scopus , accessed on

1 November 2024). They selected the most relevant and up-to-date articles in their opinion for each issue, to prepare a presentation for the meeting.

Drafting

On 11 and 12 November 2024, two medical writers (CMRL and CGC) attended and then, between November and December, they wrote a text with the main ideas exposed in the meeting.

Revision

Between January and February of 2025, all the experts had the opportunity to read the complete text and raise objections and changes.

Results

New vaccines against respiratory pathogens: the power of prevention

The best approach to illness is prevention rather than cure. Preventing pneumonia is crucial. To achieve this, it is important to maintain a good level of health throughout life. This is also important to maintain a sustainable health system as people are ageing and it is predicted that by 2100, 28% of the world's population will be 65 years old or older [11–14].

The immune system changes and matures over the course of a person's life. It works best in adulthood, but its functions decline again in old age [15–17]. This makes people more vulnerable to infectious agents in the extremes of life. There are several things that can be done to improve this, such as living a healthy lifestyle and avoiding toxins such as tobacco. Another major intervention to improve the performance of the immune system is immunisation throughout life [13,14]. The goal is to achieve a good quality of life and prevent age-related disability. In fact, lower respiratory tract infections have been the fourth leading cause of morbidity and mortality worldwide in the last 30 years, and COVID-19 was the second leading cause in 2021 [18]. Vaccines against pneumonia-causing pathogens are available and may be useful in reducing the disability and death associated with pneumonia. Surveillance systems, such as SiVIRA (Acute Respiratory Tract Infections Surveillance) can also help to demonstrate their success [19].

There was no influenza activity in 2020-21, but a very pronounced epidemic peak was recorded in 2023-24. Influenza-related hospitalisations are more common in people aged less than four years or more than 65 years [19]. These infections have a multimodal negative impact on patients, leading to increased disability and adverse neurological, metabolic, cardiovascular and respiratory events [20–23]. Moreover, vaccination rates do not reach the desired proportion of the target population [24]. This target population is made up of vulnerable people at risk of adverse events following influenza infection, as well as relatives and professionals who care for these patients [25]. Influenza vaccine is less effective than other classic vaccines, such as measles. In 2024, a tetravalent formulation has been chosen. There are newer formulations, such as adjuvanted, high-load, recombinant and made with mRNA which can achieve a better effectiveness in particularly vulnerable people. There is no difference between them, and they provide better protection than the standard formulations [26,27].

The COVID-19 vaccines were a major scientific achievement, saving more than 20 million lives in their first year of use. However, vaccination rates are falling, and in the 2023-24 campaign, the rate of people with a booster dose was 46% over the age of 60 and 64.3% over the age of 80 [28,29]. A booster dose is recommended for those at risk, as new variants emerge that are better able to evade the immune system. The immune response to natural infection or vaccination is short and variable between individuals, and vaccines adapted to current circulating variants provide better immunity [29]. For the 2024-25 season, JN.1 adapted vaccine has been chosen for the booster, it can be administered together with influenza vaccine and others, and its recommendation is independent of the number or previous doses [25].

Streptococcus pneumoniae is the third most deadly bacterial pathogen in the world, and its vaccine can save many lives [30]. In people of extreme age, the number of infections and deaths increases [31,32]. The most common serotypes vary by age group, but serotypes 3 and 8 are very common in patients aged less than one year and more than 65 years in Spain [33]. Vaccine efficacy will therefore vary according to age group and circulating serotypes, so its surveillance is very important. Objective vaccination coverage is over 95% for children and over 75% for adults [34]. There are several vaccines on the market, each with a different number of serotypes. It is not clear that, the greater the number of serotypes, the better the protection. So, the recommendation of one over the other varies between regions in Spain [35].

Respiratory syncytial virus (RSV) is another respiratory pathogen that also has a more severe impact on individuals at the extremes of age. Almost all children have been infected by the age of 2, but immunity against it is not complete and wanes quickly, so reinfection is very common. Older adults are at higher risk of developing a severe infection, especially those with

Table 1. Current and future options to prevent severe disease by respiratory syncytial virus. Adapted from Mejias A *et al*. [40].

Target population	Possible strategies
Pregnant women	Subunit vaccines. Attenuated vaccines are contraindicated.
Babies under 6 months	Monoclonal antibodies Subunit vaccines are ineffective.
Children over 6 months	Future: viral vectors and attenuated vaccines.
Older people	Adjuvanted subunit vaccines. Attenuated vaccines may be contraindicated.

Table 2. Biomarkers to guide medical acts.

Medical issue	Biomarker
Diagnosis	PCT MDW
Prognosis	Lactate PCT MR-pro-ADM
Monitoring	Lactate PCT MR-pro-ADM
Guide antibiotic therapy	PCT

PCT: procalcitonin; MDW: monocyte distribution width; MR-Pro-ADM: Mid-regional-pro-adrenomedullin.

co-morbidities [36–39]. As shown in **Table 1**, there is now a range of therapeutic arsenal to prevent serious infections [40]. In Spain, the use of nirsevimab, a monoclonal antibody against RSV, has demonstrated to be an effective intervention against severe disease in infants, with an 87% reduction in attributable hospitalisations and a 92% reduction in ICU admissions [41]. In people over 60 years of age, with comorbidities or immunosuppression, adjuvanted vaccination is an intervention that also protects against severe disease and this protection lasts for 3 years in more than 70% of people vaccinated [39,42–47].

Finally, the benefits of vaccines are not limited to preventing the transmission and severe disease of their target pathogens but also help to reduce the incidence of antimicrobial resistance by reducing the need to prescribe antibiotics, which are sometimes inappropriately prescribed for viral infections [48].

Diagnosis in severe pneumonia

Latest news on biomarkers in the management of pneumonia

Biomarkers are useful tools to guide medical actions, as can be seen in **Table 2**, but they must be used according to clinical judgement and a decision should never be made based solely on a biomarker value.

Procalcitonin (PCT) has been shown to be useful in reducing antibiotic use and duration of antibiotic treatment [49,50]. However, other researchers have reported conflicting results, probably because their target population was more likely to need antibiotics [51,52]. In a posterior meta-analysis, the use of PCT to guide antibiotic treatment demonstrated a reduction in 30-day mortality, adverse events and antibiotic exposure [53]. PCT has shown its usefulness in immunosuppressed patients [54] and to predict bacteraemia in emergency departments [55]. In fact, current recommendations for stewardship in emergency departments suggest the use of PCT to guide antibiotic initiation in patients who are likely to be admitted to hospital with either a lower respiratory tract infection, acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD) [56]. Although some researchers have found an association between high PCT levels and infection by multidrug-resistant microorganisms, this finding is not consistent along the literature and more evidence is needed [57]. To date, no biomarker can predict an infection with a multidrug-resistant microorganism.

Mid-regional-pro-adrenomedullin (MR-proADM) is a biomarker with interesting prognostic properties. Its ability to identify patients at risk of clinical deterioration has been demonstrated in several studies. It rises early in patients with future poor evolution in the next 24-48 hours, when the clinical examination and the rest of biomarkers are still normal. Its performance to identify these patients is better than scores, such as NEWS-2 and SOFA, and lactate [58,59], even in immunosuppressed patients [60]. Combining MR-proADM measurement with other scores or measures does not improve its yield [61]. It also provides information independent of that provided by PCT, as high persistent levels of MR-proADM are associated with poor prognosis, despite decreasing levels of PCT [59].

The timing of taking blood samples to determine biomarker levels is very important, as it may take several hours to reach levels that indicate a bacterial infection. This is particularly important for PCT. If a blood sample is taken too early in the course of the disease, it can result in a false negative. So sometimes it is necessary to take a new blood sample 6 hours later to ensure a low level of a biomarker [62]. Patient characteristics are also important. In older adults, C-reactive protein (CRP) and white blood cell count are useless for infection management, although PCT retains its utility [63]. Using breakpoints in biomarkers like PCT could help in the decision-making process. However, more important is their tendency over time to be interpreted to guide therapy and predict clinical evolution [64].

From antimicrobial stewardship to diagnosis stewardship and vice versa. Implications in pneumonia

Antimicrobial stewardship programmes (PROA) are multidisciplinary projects that have emerged in response to the steady increase in micro-organisms resistant to various antimicrobial agents, particularly in pneumonia, with the aim of improving clinical outcomes, minimising adverse effects, preserving the hospital and community ecology and reducing the costs of antimicrobial use. At the same time, the Microbiological Diagnosis Optimisation Programmes (PRODIM) are actions aimed at optimising the use of available diagnostic techniques in a coordinated manner, promoting appropriate therapeutic, clinical and preventive decisions, adjusted to cost-effectiveness. Both PROA and PRODIM are direct tools for optimizing diagnostic and antimicrobial resources with a direct impact on patient health and the healthcare system. They also allow the clinician to make appropriate decisions, oriented as recommendations, which promote an optimized use of antimicrobial therapy [65]. Both programmes should be adapted to the work centre, with the approved recommendations of each commission of the Emergency Department, Pharmacy, Microbiology, Infectious Diseases Unit, ICU or any other service, adapted to the guidelines of the different Autonomous Communities and the management that supervises it [66]. PROA and PRODIM work together to establish a syndromic diagnosis to define an empirical treatment for pneumonia. To do so, they must rely on the microbiological diagnosis together with the available syndromic platforms, thus obtaining a targeted treatment for the appropriate time [67]. It is important to classify the patient according to whether it is severe CAP, HAP (or VAP), or whether it is a case of pneumonia in an immunosuppressed patient.

In severe CAP, blood culture collection is indicated when there are risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant gram-negative bacteria (GNB), although their sensitivity is low (4-16%). Thus, they have low impact on changing empiric therapy. Culture and Gram staining of respiratory specimens allows targeted therapy according to antibiogram (24-48h) and allows de-escalation when MRSA or BGN are not detected [68]. Currently, due to the existence of rapid multiplex protein chain reaction (PCR) and respiratory virus antigen tests, they allow a rapid diagnosis of CAP when the aetiology is viral, reducing the use of antibiotics. The use of urinary antigens of *S. pneumoniae* and *Legionella* serogroup 1 are widely commercialized, these should be used according to clinical and in case of suspicion of *Legionella*, request it according to epidemiological history [69]. In HAP, it is advisable to perform quantitative cultures when invasive samples (bronchoscopy sample or bronchoalveolar lavage-BAL-) can be obtained, although non-invasive samples (sputum or tracheal aspirate) can be of great relevance when invasive tests are not available. The use of syndromic panels is a complementary tool to conventional microbiological techniques as it decreases the time to appropriate antimicrobial therapy and has a direct impact on antibiotic consumption. In patients with HAP and VAP, it is advisable to use syndromic panels regardless of risk factors for multidrug-resistant bacteria or shock (always in combination with conventional techniques) allowing treatment to be adjusted according to the results of the panel (in patients with hemodynamic stability, delaying treatment until results are available (< 3 hours) can be considered) [70]. In the immunosuppressed patient pneumonia, the probability of fungal infection must be taken in addition to the usual pathogens. Therefore, techniques such as galactomannan antigen (GM) detection (to detect *Aspergillus* spp.) or β-D-glucan (to detect *Candida* spp., *Aspergillus* spp., *Pneumocystis* or *Fusarium* spp.) should be used in a complementary manner on respiratory or blood samples to confirm the presence of fungal pneumonia [71].

Interpretation of molecular diagnostic results in the management of pneumonia

The use of syndromic panels for the detection of microorganisms and resistances in respiratory samples has been a great advance in the diagnosis of CAP, HAP and VAP. Standard methods frequently fail to identify the infectious aetiology due to the polymicrobial nature of respiratory specimens and the need to order specific tests to identify other viral and atypic agents. The potential severity of these infections, combined with the inability to clearly identify the

causative pathogen, leads to the administration of empirical antibiotics based on clinical presentation and other risk factors [72].

PCR multiplex panels present an increased detection yield compared to standard culture, with high negative predictive value of targets and high positive predictive value for genotypic markers of resistance. Commercialised PCR multiplex panels can be used with different sample types (sputum, BAL or bronchial aspirates) providing results within a few hours and allowing targeted treatment [73]. However, despite its wide use, culture remains the gold-standard technique. However, there are still uncertainties regarding the clinical interpretation of some results [74]. For example, the correlation between genome copies per mL and Colony Forming Units (CFUs) per mL could be difficult to interpret because it depends on several factors such as the type of sample, the semi-quantitative value obtained, and the type of microorganism detected. Despite the number of microorganisms and resistance genes already present for detection, there are still some pathogens of interest such as *Stenotrophomonas maltophilia*, virus and some fungi (*Aspergillus* spp.) that are not yet available in all of these platforms. Despite these drawbacks, these platforms represent a great advantage in the decision of empirical treatment in patients with CAP, HAP, VAP and especially, in those patients with multidrug-resistant risk factors [75].

GEIPC-GTEIS recommendation document of syndromic platforms for pneumonia in critically ill patients

The need for a consensus document for considerations for the use of syndromic platforms is increasingly evident in the day-to-day clinical practice and diagnosis of pneumonia. A Rapid Multiplex Syndromic Molecular Panels (RMMSP) is a platform that can detect 3 or more pathogens and resistance mechanisms. There are a lot of RMMSP marketed in the European Union and/or approved by the Food and Drug Administration (FDA). To this end, the main objective of this work was to review the available scientific evidence on their use, the time until a microbiological diagnosis is available, and the management of the main infections in critically ill patients: pneumonia, bacteraemia-fungaemia, meningitis/encephalitis and off-label applications of syndromic panels. The participation of GEIPC (Study Group on Infections in Critical Patients)-SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology) and GTEIS (Infectious Diseases and Sepsis Working Group of Spanish Society for Intensive Care Medicine) -SEMICYUC (Spanish Society of Critical Intensive Medicine and Coronary Units) as collaborating working groups in the systematic review of the literature published up to the date of publication of the study was essential [76].

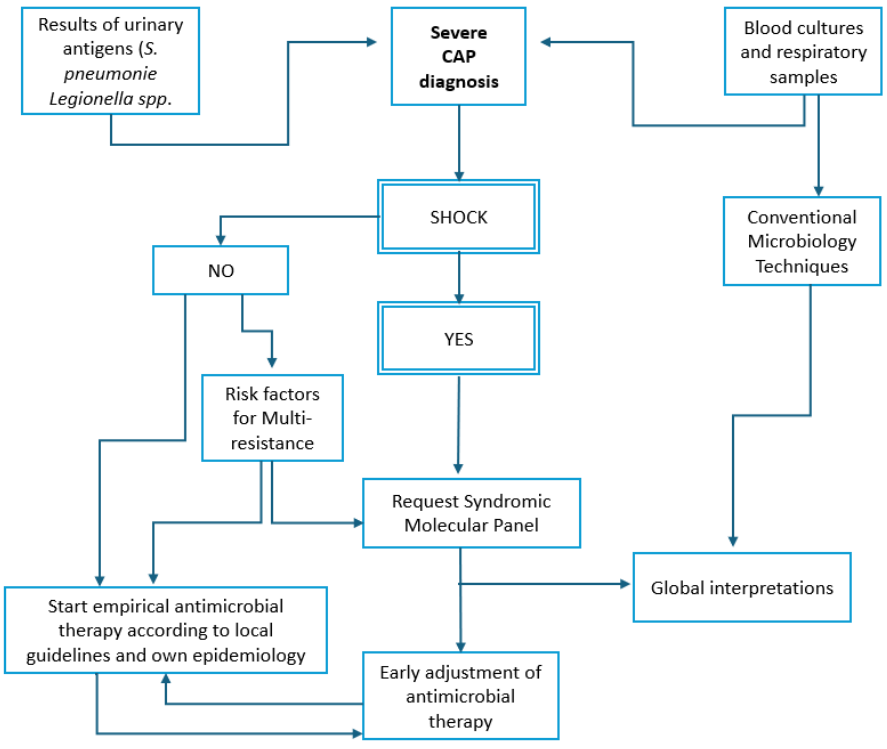

Figure 1. Algorithm for the use Rapid Multiplex Syndromic Molecular Panels of in severe community-acquired pneumonia. Adapted from Candel F.J. *et al* [76].

This document shows in detail the most widely marketed RMMSP used for the different types of infection for which they are intended, presenting their targets, their main advantages and disadvantages. Furthermore, it provides scientific evidence on potential clinical impact of the use of syndromic pneumonia molecular panels on patients with HAP/VAP and multi-drug resistant (MDR) CAP patients. These patient profiles can benefit from being tested by a pneumonia syndromic platform including genotypic resistance marker targets. Another major challenge in using RMMSPs is how to interpret their results: qualitative versus quantitative and implications for culture results. However, despite the great help that these platforms can provide in the rapid diagnosis of pneumonia, they still cannot replace conventional microbiological culture. They are highly sensitive tests with a very high negative predictive value, but they can detect non-viable genetic material or detect microorganisms that do not cause infection, such as colonizing bacteria. The information provided by the RMMSP must be agreed upon in a multidisciplinary manner to make appropriate decisions for the choice of a well-founded antibiotic treatment [77–79].

The result of an RMMSP alone should not be used for diagnostic guidance; factors such as the patient's condition, results of colonization studies, previous and current antibiotic therapy, and additional conventional microbiological tests must be considered [80]. Several observational studies suggest that the use of RMMSP in critical ill patients with HAP/VAP and MDR organism-CAP increased the diagnostic yield, leads to a reduction in the time to appropriate antimicrobial therapy and decreases antibiotic consumption [81–83]. All this evidence has allowed us to develop a flowchart for the optimal indication of this type of tests in pneumonia as can be seen in **Figure 1**.

Zero Resistance

Impact of Zero Resistance programme in pneumonia

Zero Projects and *Envin* (National Surveillance Programme for Nosocomial Infection) have had a profound impact on patients' safety in the ICU. They have led to a reduction in the incidence of VAP and device-associated infections. They are also likely to have improved survival, length of stay in intensive care and disability. Moreover, these programmes have raised awareness among healthcare professionals and managers. As a result, we now have a lot of data to evaluate our practices and to improve them further [84–90].

Increased knowledge about infections in the ICU has also improved clinical practice [84,85]:

- Identification of MDR carriers allows for reduced transmission of these microorganisms in the ICU, improved empirical choice of antibiotics and targeted therapy.
- A high proportion of MDR carriers in the ICU were present on admission, and these MDR were not acquired in the ICU.
- Enables better monitoring of MDR in the ICU.

The *Envin-Helics* report [87] is a national study of Spanish ICUs. It shows a decrease in median length of stay and crude mortality. It also shows a reduction in hospital-acquired infections and VAP rates. However, VAP remains the most common hospital-acquired infection. Trends in the use of antibiotics are also positive: their use was less frequent, empirical treatment was more often adequate, cultures were taken more often before antibiotics were prescribed, and changes in antibiotic therapy to reduce the spectrum were more frequent. However, meropenem, piperacillin-tazobactam, and linezolid remain the most prescribed antibiotics. The most isolated microorganisms are the same as usual: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *S. aureus*, *S. maltophilia,* and *Escherichia coli*.

Envin surveillance began in 1994, and Zero Projects began their implementation in 2009. Since then, the incidence of ICU-acquired VAP has steadily decreased until 2016. This rate remained low and stable until the COVID-19 pandemic, when an increase was observed. In the last two years, the trend has been decreasing again, but we are now above the desired rate of 7 cases per 1000 days of mechanical ventilation [87].

Finally, the results of national surveys, give a good picture of declared compliance with Zero Pneumonia and Zero Resistance [84,85,91,92]. The main weakness is the routine molecular identification of MDR bacteria. Identified barriers to the implementation of Zero Projects are learning programmes, care overload, burnout and high staff turnover rates.

Selective decontamination of the digestive tract in the prevention of VAP

Selective decontamination of the digestive tract (SDD) was first studied by Stoutenbeek et al. in 1984. They described the effect of administering non-absorbable oral antibiotics and cefotaxime intravenously (IV). Patients with SDD who received this regimen had a lower number of bacteria in their oropharynx and rectum at the end of follow-up, whereas controls had a

Table 3. Selective decontamination of the digestive tract protocol. Adapted from *Proyecto Neumonía Zero* [95].

Timing of SDD	Regimen			
	Oral paste	**Digestive solution**	**IV antibiotic**	**Anti-MRSA therapy**
As early as possible, when a patient is planned to be in MV more than 48 hours	After adequate oral hygiene, the health care professional will administer chlorhexidine 0.12-0.2% oral paste	Oral administration of non-absorbable antibiotics by tablet or nasogastric tube. The most common combination is neomycin, nystatin and tobramycin	Administration on third generation cephalosporin for 3 or 4 days.	If the patient is colonised with MRSA, add: - antiseptic nasal ointment and - IV vancomycin

SDD: Selective decontamination of the digestive tract, MV: mechanical ventilation; IV: intravenous; MRSA: methicillin-resistant *S. aureus*.

higher rate of colonisation, with a change in oropharyngeal flora from a net predominance of gram-positive bacteria at the beginning of follow-up to almost 100 percent gram-negative colonisation at the end. In addition, patients with SDD experienced a lower rate of infection [93].

Since then, much research has been done to replicate these results and tailor the best therapy for different types of patients. Changes in the lung microbiome are caused by bacterial translocation from the gut and facilitated secretion aspiration in sedated patients, related to muscle-induced paralysis, type of diet, use of anti-gastric secretagogues and immune dysfunction [94].

SDD is the tenth recommendation of Zero Pneumonia Programme [95]. It has a strong level of evidence, and its grade of recommendation is also strong. Complete SDD is preferred, although oropharyngeal topical decontamination alone is used in patients who are unable to receive oral medication due to a compromised digestive tract. The complete protocol can be seen in **Table 3**.

Several SDD regimens have been investigated in the past:

- In a meta-analysis, Pileggi *et al*. described a 27% reduction in infection rate with selective oropharyngeal decontamination (SOD) alone and a 36% reduction with a combination of topical decontamination and intravenous antibiotics (SDD), both compared with controls. There was no difference in mortality [96].
- In another meta-analysis of randomised controlled trials, Zhao *et al*. found that there was no difference in mortality in ICU patients between SOD alone and SDD, but surgical patients had a lower mortality rate with SDD. SDD also reduced the number of bacteraemia episodes and the isolation of resistant microorganisms, compared with SOD [97].
- In a recent clinical trial, 90-day mortality was the same in patients receiving SSD or placebo, but patients receiving SSD had fewer resistant microorganisms, positive blood cultures, and *C. difficile* diarrhoea [98].
- Finally, in a Cochrane review, Minozzi et al. found a reduction in mortality and lung infections in patients treated with SDD compared with placebo, whereas SOD showed only a lower rate of lung infections and no difference in mortality compared with placebo. Therefore, the greatest benefit is achieving through a combination of oral topical antiseptics, digestive decontamination, and systemic antibiotics (SSD) [99].

There are some subgroups of ICU patients who may benefit more from SSD, as shown in **Table 4** [100–106].

Despite these benefits, there are barriers to its implementation, including the difficulty of preparing oral formulations (commercial formulations are now available), economic cost, nursing workload and the potential for the development of antimicrobial resistance. However, the incidence of isolation of MDR microorganisms decreases with the use of SDD. Moreover, SDD is also associated with reduced antibiotic consumption [107–110]. Finally, considering all possible interventions to reduce VAP, SDD is the only intervention supported by highly suggestive evidence and is responsible for the 41.18% of the risk reduction [111].

Zero Resistance Document Update Project. GTEIS-GEIPC collaboration

As mentioned in the previous section of this work, the main objective of the Zero Pneumonia project is to reduce by 20% the rate of patients in whom one

Table 4. Effect of selective digestive tract decontamination compared to placebo in different types of ICU patients.

Type of ICU patient	Systemic antibiotics	Benefit in mortality	Benefit in RI	Other benefits
Brain injuries	Yes	Yes	Yes	Fewer rate of *C. difficile* infection, resistance and positive blood cultures
Major heart surgery	No	No	Yes	Fewer rate of colonization with *Pseudomonas*
Elective gastrointestinal surgery	Yes	Not determined	Yes	Fewer rate of suture dehiscence, wound infections and infectious complications
Burn	Yes*	Yes	Yes	-
Medical and surgical	Yes	Yes	Not determined	No difference between medical and surgical patients
MV	Yes*	Yes	Yes	Fewer rate of bacteriaemia, stay in ICU, days with VM

ICU: intensive care unit; RI: respiratory infections; MV: mechanical ventilation.
*These studies compared, also, regimens with and without systemic antibiotic. Patients with systemic antibiotic had better outcomes.
Adapted from Young PJ *et al,* Pérez-Granda MJ *et al*, Roos D et al, Rubio-Regidor M *et al,* Plantinga NL *et al*, Hammond NE *et al,* and Pérez-Torres D *et al.* [100–106].

or more multidrug-resistant GNB are isolated during their stay in the ICU [112]. The secondary objectives of this project are to describe the map of multidrug-resistant GNB acquired in the Spanish ICUs, promote and reinforce the safety culture in this type of Units and create a network of ICUs, through the different Autonomous Communities, that apply safe practices of proven effectiveness [113]. This project was implemented between 2014 and 2016 [113]. It is worth noting that the rate of multidrug-resistant GNB in patients at participating centres has decreased by 16% [114].

However, the initial proposals had to be updated due to the changes that arose during the years after their implementation. During this period, similar projects have been updated because of new scientific evidence, better understanding of resistance, implementation of PROA/PRODIM-type programmes and progress in the control of new pathogens causing outbreaks. The following changes were proposed as promising new content to relaunch the project:

- To identify new pathogens that were not initially considered in 2014;
- To determine when contact precautions should be taken and for how long;
- To define the role of molecular techniques for rapid microbiological diagnosis;
- To implement new devices or strategies to fight outbreaks and special endemic situations.

With this, they aimed to determine whether isolation is required for typical resistant bacteria and new species, such as azole-resistant *Candida spp.* or *Candida auris*. The criteria involved in the antibiotic use policy (including new antimicrobials), the type of action plan to determine colonized patients, and developments in the detection of cross-resistance with specific identification of reservoirs in the ICU were also updated. For its preparation, an updated review of the scientific evidence on the discussed topics was conducted [114,115].

In this way, new project recommendations will be defined according to a specific multidisciplinary work plan in collaboration with GTEIS and GEIPC. They will be published by the second half of 2025.

Pneumonia in different clinical settings

Aetiopathogenesis and therapeutic implications of pneumonia and pneumonitis in patients with thoracic solid tumours

To understand the etiopathogenesis and implications of pneumonia in patients with solid thoracic tumour, general risk factors for immunosuppressed patients can be used. The probability that these types of patients suffer an opportunistic infection or reactivation of a latent infection increases with their immunosuppressed state. In addition to the conventional agents that cause pneumonia in non-immunosuppressed patients (*S. pneumoniae*, *S. aureus*, *H. influenzae*, GNB), in patients with a weakened immune system the probable participation

of other microorganisms such as *Nocardia* spp., non-tuberculous mycobacteria, respiratory viruses, and even agents that cause fungal pneumonia should be taken into account, such as *Aspergillus fumigatus* or *Pneumocystis jirovecii* [116]. In some cases, multidrug-resistant pneumonia-causing agents must also be considered, since these patients suffer repeated admissions, cycles of antibiotics, and colonization by multidrug-resistant GNB [117].

To identify the causative agent of pneumonia, conventional microbiological techniques must be used, such as culture of respiratory samples, urinary antigens and blood cultures [118]. In recent years, in addition to multiple syndromic platforms for the detection of the main pathogens that cause pneumonia and their possible resistance, specific PCRs have been developed to be performed on respiratory or whole blood samples (for cytomegalovirus -CMV-, Epstein Barr virus, respiratory viruses, or fungi). The use of β-D-glucan or galactomannan antigen are available alternatives when invasive fungal infection (IFI) is suspected [118]. Despite the battery of tests available for the diagnosis of pneumonia of infectious origin (including radiological and clinical tests), the onset of pneumonitis can be difficult to differentiate [117–119].

Pneumonitis arises as an inflammatory phenomenon in patients with solid thoracic tumours in response to exposure to radiotherapy, chemotherapy or immunotherapy [120]. It is important to make a differential diagnosis between pneumonia and pneumonitis due to the selection of targeted treatment [121]. Both may even coexist in complex patients. Differential diagnosis between these processes is difficult because they share some diagnostic features. In general, the use of microbiological tests is indicated for the diagnosis of infectious pneumonia; it can also be used to rule it out [122]. For the diagnosis of pneumonitis, microbiological tests with an individualized clinical diagnosis should also be used [123]. The diagnosis of pneumonitis may be accompanied by anatomopathological study of transbronchial biopsy samples, although in most cases this type of sample is difficult to obtain [124].

The treatment of pneumonitis is mainly based on the use of corticosteroids. These drugs act as immunosuppressants, so it is crucial to rule out suspicion of infection. The use of corticosteroids concomitantly with an infectious process can markedly aggravate the situation. On the other hand, a pneumonitis process not treated due to confusion with an infectious process will cause a worsening of the inflammatory situation [121,122,125]. Therefore, the differential diagnosis of pneumonitis and infectious pneumonia in patients with solid thoracic tumour is key to act quickly to achieve therapeutic success.

Aetiopathogenesis and therapeutic implications of pneumonia in immunosuppressed patients: solid organ transplantation, onco-haematological diseases, treatment with corticosteroids

Pneumonia in immunosuppressed patients has become common in clinical practice due to the increase in the number of immunosuppressed patients. Immunosuppression may be caused by the oncological disease, its treatment, immunosuppressive drugs such as corticosteroids, concomitant viral infections or previous transplantation [126]. Patients may show classic or atypical patterns of pneumonia on radiological findings. Some of the common ones are the presence of nodular (or micronodular) lesions, cavitations, glass-like opacifications, consolidations or pleural effusion [126]. It is important to be able to know the causative agent of pneumonia and differentiate it from other causes such as chemical pneumonitis due to gastric acid aspiration, tumour expansion or pharmacological pneumonitis [127]. Pulmonary infection can arise as CAP, HAP, VAP, associated to radiotherapy, opportunistic infection or of aspiration origin [128]. The use of Chimeric Antigen Receptor T-Cell (CAR-T) therapies and the concomitant use of check point inhibitors contributes to increase the risk of infection in these types of patients, mainly increasing the risk of pneumonia as a complication [129]. The findings in radiological tests can be broadly divided into two groups: signs of angioinvasiveness and signs of invasion of the airway itself.

Regarding the signs of angioinvasiveness, it is worth highlighting these features:

- The air crescent sign, which may be suggestive of invasive aspergillosis although it may be confused with bronchial tumours;
- Monod sign: air surrounding a fungal mass in a pre-existing cavity, compatible with aspergilloma;
- Halo sign: it may present as a solitary pulmonary nodule or a mass surrounded by opacity with a ground-glass appearance, mainly compatible with amyloidosis, mucormycosis, sarcoidosis or vasculitis;
- Reverse halo sign: presented as a ground-glass opacity consolidation, consistent with sarcoidosis, paracoccidiomycosis, or lipoid pneumonia.

As the main finding of airway invasion, the tree-in-buds sign should be highlighted. It is shown as the presence of multiple centrilobular nodules grouped in a linear branching pattern. This radiological image is compatible, among other causes, with viral bronchiolitis, aspiration pneumonia or infection by non-tuberculous mycobacteria. However, in many cases

patients do not show these features or they are not easily recognizable [127,130].

In addition to empirical coverage of conventional bacteria, when we suspect pneumonia in the immunosuppressed patient, the probable infection or reactivation of viruses such as CMV, herpes virus and other viruses such as influenza, adenovirus and SARS-CoV-2, or atypical bacteria must be considered [131–133]. Furthermore, this type of patient is more susceptible to IFI, mainly due to *Pneumocystis jirovecii* and *Aspergillus spp.* There are factors that increase the probability of IFI. The main ones are neutropenia (<500/mm3), haematological malignancy, allogeneic bone marrow transplant, therapy with ibrutinib or corticosteroid therapy (>0.3 mg/kg/day, for more than three weeks) [134,135].

Given the high likelihood of infection in this type of patient during their treatment, procedure or hospital stay, it is advisable to assess risk factors on an individual basis so that prophylactic or empirical treatment can be determined in the event of pneumonia or the risk of developing it. [136]. In general, these patients must be vaccinated, with an updated serological study, with multidisciplinary follow-up in order to anticipate possible cases of pneumonia, especially in those patients who start immunosuppressive therapy [137]. Empirical treatment should be as individualized as possible until it can be directed with microbiological results when they are available [135].

Aetiopathogenesis and therapeutic implications of pneumonia in the elderly

Ageing is a poorly understood process by which living organisms deteriorate over time. In humans, nutritional deficiencies, mental state, exercise and genetic aspects are involved in this process [138]. The proportion of the population aged over 60 in Spain has increased from 8.2% in 1960 to a projected 26.2% in 2030. The proportion of people aged over 80 is also increasing and is projected to reach 13% of the total European population in 2080 [139]. Pneumonia is a very important disease in the elderly because its incidence increases with age, almost half of all pneumonia cases occur in people over 65. It is the leading cause of sepsis in the elderly, 75% of elderly people with pneumonia require hospitalisation and 10-20% need admission to intensive care. It is the sixth cause of death in the elderly, with a mortality rate 25% higher than in younger people. Three-hour sepsis bundle compliance in the ED is associated with longer survival in sepsis patients aged 65 years or older. Pneumonia also causes a reduction in quality of life and, finally, it represents a major economic burden on the health system [140–144].

But it is not just the biological aspects that are important. Patients' personal preferences must be considered in the decision-making process [145]. Hospital-associated disability is a real problem, affecting one in two old people who require hospitalisation [146]. This risk is greater for frail people, as frailty is a marker of biological age and its associated vulnerability to worse outcomes, in contrast to chronological age [147]. The performance of frailty scales, such as the Clinical Frailty Scale, the Functional Index - Emergency, or the Identification of Seniors at Risk scale, which are useful tools for identifying frail older patients at high risk of developing an adverse outcome (death, functional decline, hospitalization, or revisiting the ED) within 30 days after hospital discharge [148].

Furthermore, immune system function declines with age, with both innate and adaptive immunity functioning worse [16,149]. All these elements form a complex network of interactions that make a frail patient more susceptible to pneumonia and its complications [140–143,147,149–151], as can be seen in **Figure 2**.

The aetiology of pneumonia is similar in all age groups. However, co-morbidities, old infections such as tuberculosis, and previous antibiotic pressure can facilitate infection by unusual microorganisms such as viruses, mycobacteria and fungi [152]. In addition, as have been mentioned previously, viral infections such as influenza, can facilitate bacterial pneumonia, loss of autonomy, and endocrinologic and cardiovascular events [20–23]. Pneumococcal pneumonia has also been associated with an increased rate of cardiovascular events [153]. So, clinical complications in pneumonia in the elderly are frequent. They may be caused by a failure of initial treatment (**Figure 3**) or be related to the complexity of the elderly patient (**Figure 4**).

Treating these patients is also complex. It must consider factors such as the patient's clinical condition, previous co-morbidities and social and economic environment. All these factors must be combined with the patient's personal preferences to respect their beliefs and expectations. Most of these patients are polymedicated, so drug-drug interactions are very common. These must be considered when prescribing antibiotics to avoid adverse events (**Table 5**). Additionally, age-related physiological changes make these patients more susceptible to side effects [154].

Finally, prevention of pneumonia is essential to avoid these adverse events. Non-pharmacological interventions such as smoking cessation, good hand hygiene and the use of face masks have been shown to be

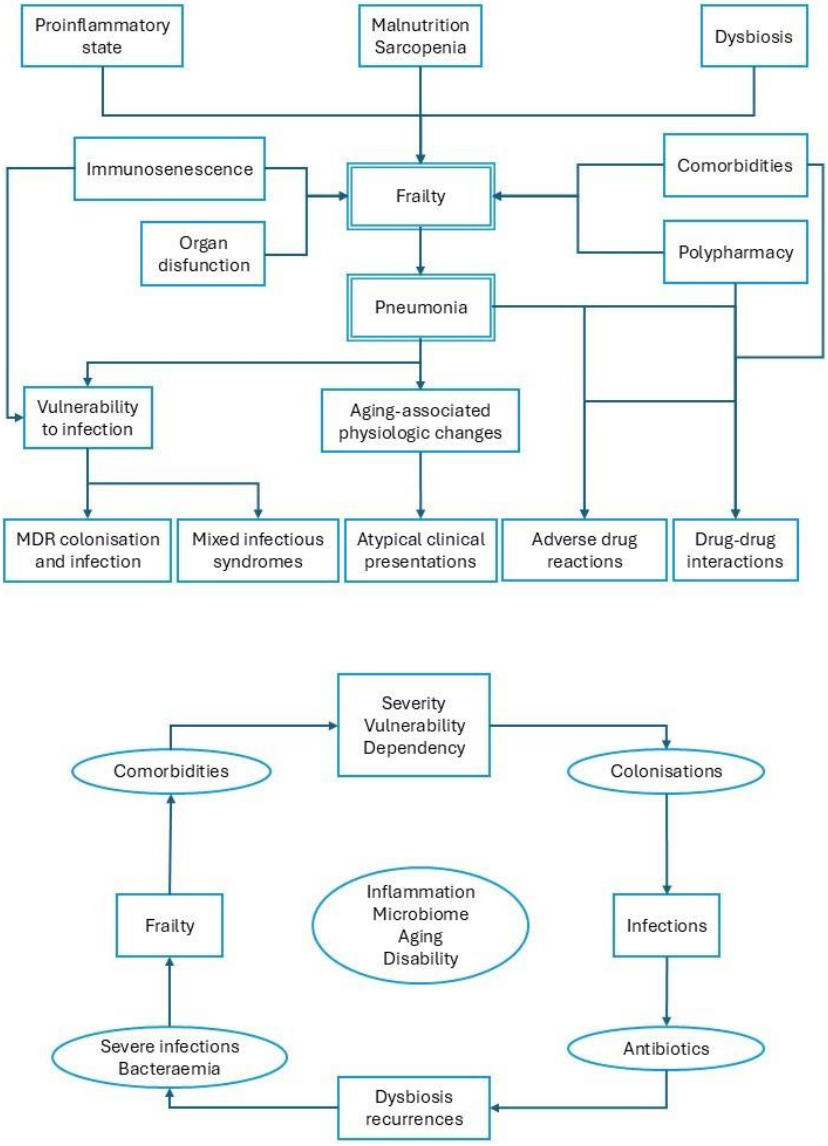

Figure 2. Complex interactions between aging, frailty and pneumonia. Adapted from Torres OH et al, Henig O et al, Cillóniz C et al (2013), Cillóniz C et al (2018), Martín-Sánchez FJ et al, Cillóniz et al (2020), Rodríguez-Leal CM et al, Candel FJ et al. [140–143,147,149–151].

useful. Good nutrition and regular exercise also help prevent frailty. Vaccination programmes have also been shown to be an effective tool for prevention [13,14,155].

Current topics in severe pneumonia

Pharmacodynamic optimisation of antimicrobials in severe pneumonia. Special situations

In HAP/VAP, appropriate therapy requires not only the selection of the correct antibiotic, but also the optimal dose and route of administration to ensure that the antibiotic reaches the site of infection [156]. A classic example is vancomycin, an antibiotic with good in vitro activity against *S. aureus* but poor clinical results because lung parenchyma concentrations are only one-sixth of serum concentration [157,158]. Fortunately, novel beta-lactams and beta-lactam with beta-lactamase inhibitor combinations have excellent lung parenchymal penetration [159].

However, not only the pharmacokinetic properties of antibiotics are important, but also the patient's condition, the microorganisms involved, the model of infection and previous treatments (**Figure 5**). Perioperative atelectasis worsens antibiotic penetration into lung parenchyma [160]. Pneumonia is a high inoculum infectious disease. This means that there are large numbers of bacteria in the tissues, and this can affect the effect of antibiotics. Cefiderocol and imipenem-relebactam are severely affected, while others, such as ceftazidime-avibactam, remain mildly affected [161]. However, for some antibiotics such as cefiderocol, this *in vitro* inoculum effect may not be clinically significant [162].

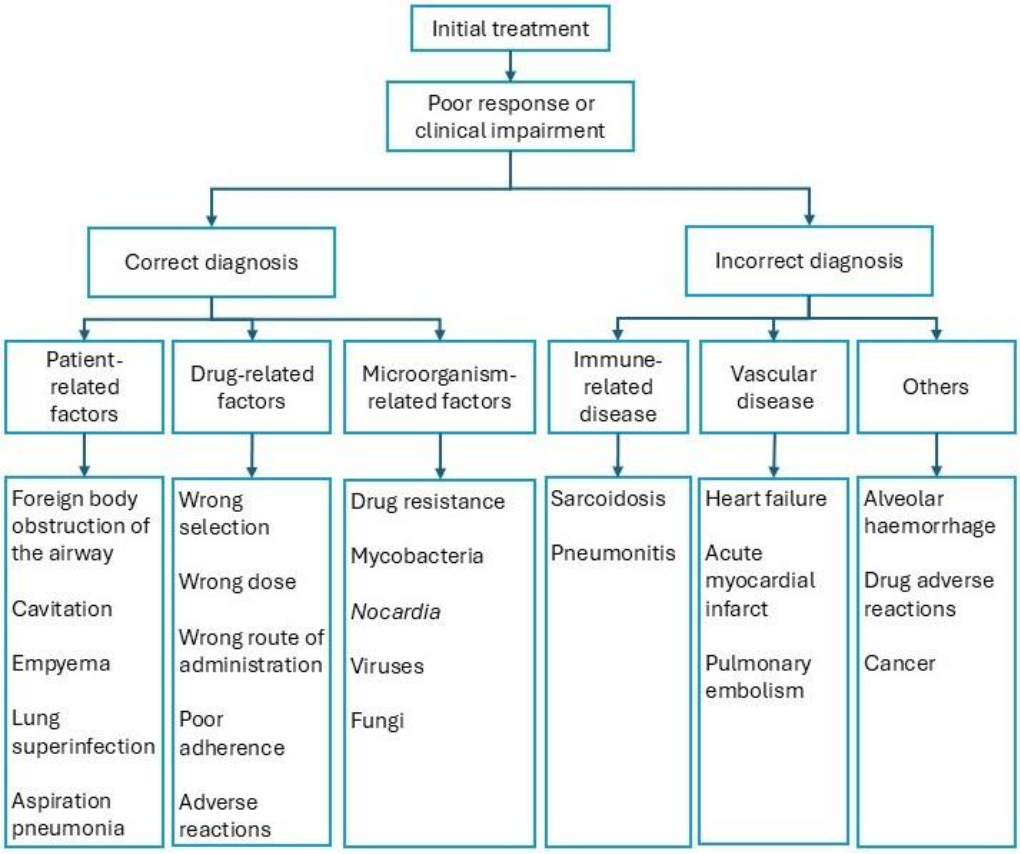

Figure 3. Differential diagnosis of treatment failure.

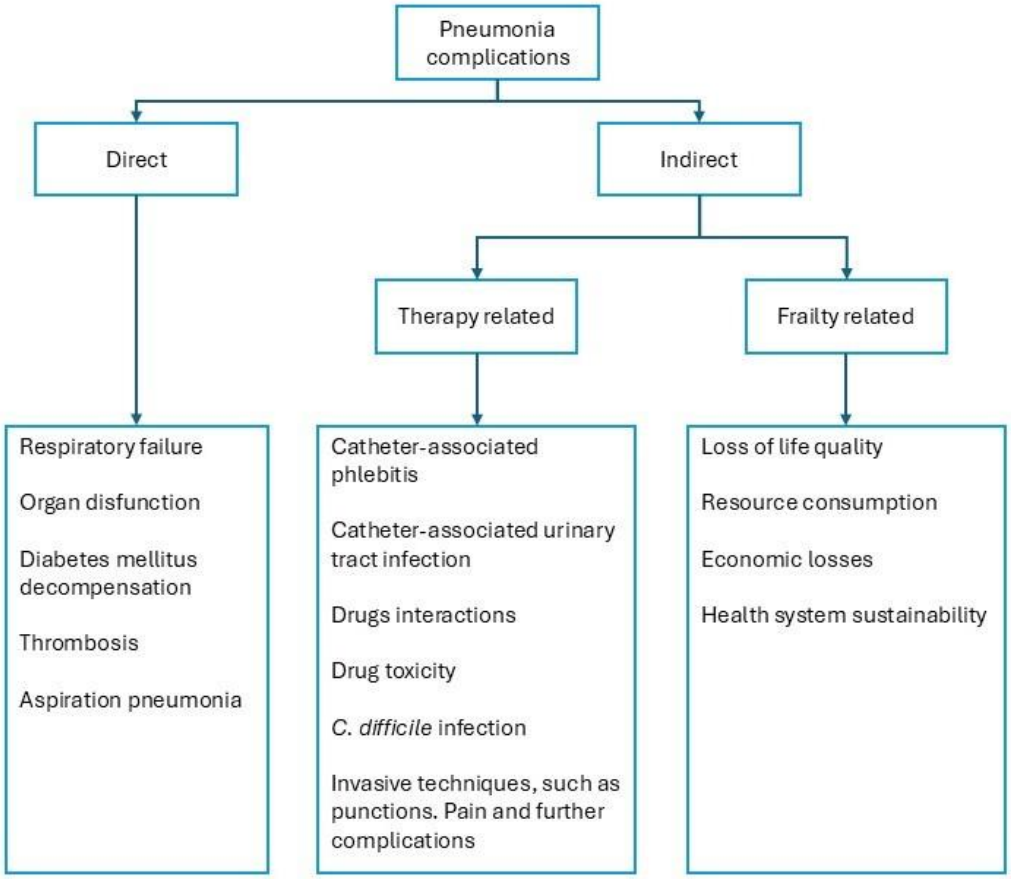

Figure 4. Complications of pneumonia in the elderly.

Table 5. Age-related risks of IV antibiotics. Adapted from Corsonello et al [154].

Antibiotic family	Age-related mechanism	Associated risk
All	Faecal incontinency	Antibiotic-related diarrhoea: falls, ulcers
Beta-lactams	Impaired elimination	Supratherapeutic levels, especially in IV route
Macrolides and quinolones	Impaired elimination	Supratherapeutic levels, especially in IV route
	CYP450 inhibition	Drug-drug interactions
	Interval QT prolongation	Cardiac arrhythmias
Quinolones	Cognitive impairment	Cognitive alterations
Aminoglycosides, vancomycin, and amphotericin-B	Impaired elimination	Reduce dose and monitor concentrations
Rifampicin, azoles	CYP450 alteration	Risk of inefficacy or toxicity
Beta-lactams, amphotericin-B	Disfunction of renin-angiotensin-aldosterone system	Hypokalemia

IV: intravenous; CYP450: Cytochrome P-450.

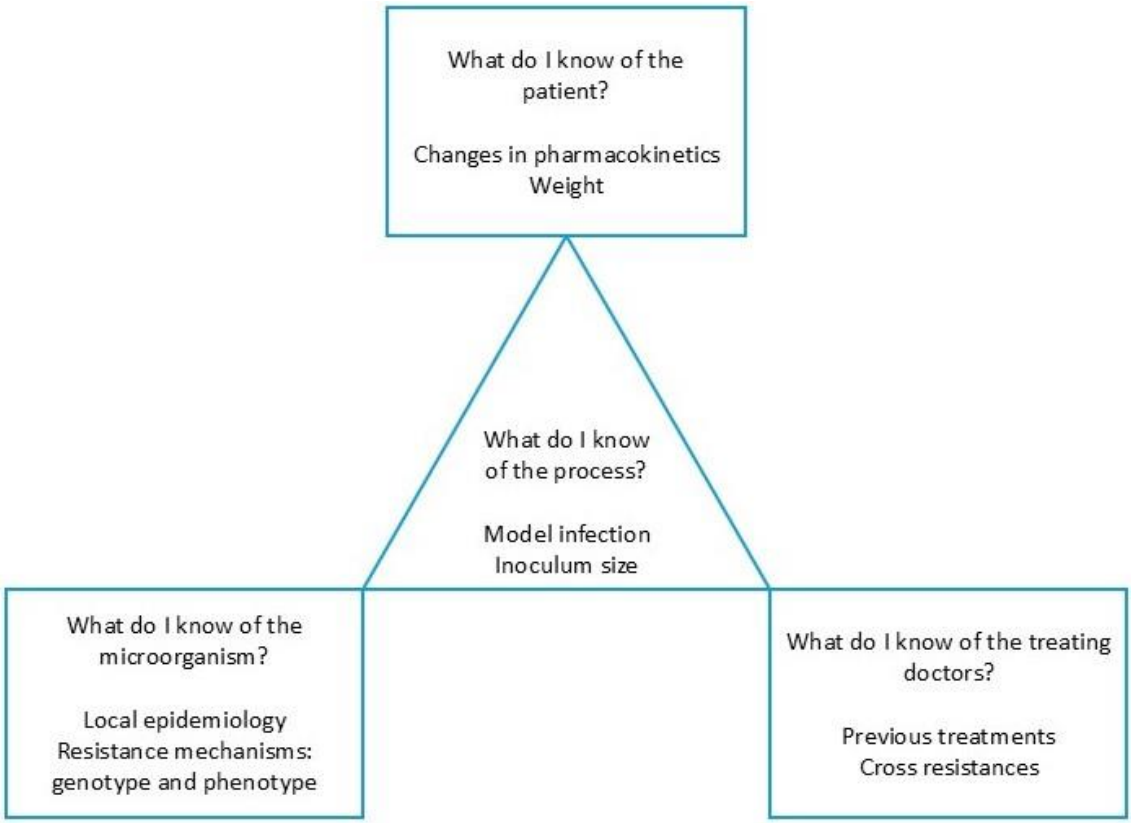

Figure 5. Factors to consider when choosing antibiotics for septic shock.

Real-world patients are not usually included in clinical trials. Obesity affects one in five patients and is associated with antibiotic treatment failure [163]. Pharmacokinetic evidence suggests that excess body fat may increase volume of distribution and clearance of antibiotics [164].

Critical illness may also impact pharmacokinetic properties of antibacterial drugs in unexpected ways. On the one hand, augmented cardiac output, capillary leakage and volume resuscitation can reduce plasma concentrations. On the other hand, end-organ dysfunction (kidney or liver) can increase plasma

concentrations. Altered protein binding may decrease or increase plasma concentrations, depending on the type of drug [165,166]. Amikacin does not reach enough therapeutic levels in 33% of critically ill patients due to initial resuscitation [167]. Beta-lactams can also be affected by increased renal clearance, resulting in lower therapeutic levels than predicted [168,169].

Several strategies have been proposed to optimise antibiotic dosing in critically ill patients. For beta-lactams, a loading dose followed by continuous infusion has the best pharmacokinetic profile [170]. This property has demonstrated a clinical benefit in terms of mortality for piperacillin-tazobactam against *P. aeruginosa* produced infections in critically ill patients [171]. Recently, an international consensus for the use of prolonged-infusion beta-lactam antibiotics has been published. They recommend a prolonged beta-lactam infusion with a loading dose to improve patients' prognosis [172]. In 2024, further evidence has been published to support this practice, showing a net benefit in terms of mortality and providing recommendations for its correct use [173–176].

Evidence for and importance of surveillance studies of colonisation in the ICU

The role of surveillance of carriers of multidrug-resistant bacteria have become increasingly important. VAP-attributable mortality in Spanish ICUs in 2023 ranges from 20 to 44.8%, depending on the severity of the patient being treated [177]. In general, patients colonised in the oropharyngeal area, and to a lesser extent by colonisation of the gastrointestinal tract, develop VAP by microaspiration or may develop bacteraemia by intestinal translocation [178]. Another possible route of transmission of multidrug-resistant bacteria is direct contact with the environment, contaminated water reservoirs, personnel handling other colonised patients or during intravenous device changes. The ability of bacteria to form biofilms is a very important factor to consider for the selective decontamination of colonized patients [179]. Active surveillance involves the systematic search for pathogens in patients regardless of symptoms. This approach makes possible to detect asymptomatic carriers who could act as reservoirs of infection. Passive surveillance, on the other hand, is performed when symptoms are present and the patient shows signs of infection, but not necessarily for asymptomatic colonization [180]. This may be less effective in containing outbreaks. Active search records 1.69 times more colonisations than passive search. However, they have not been shown to reduce the mortality rate. The culture of these bacteria for the surveillance of carriers in ICU allows to measure the incidence and prevalence in an individualized way to guide the empirical treatment. This knowledge also makes possible to comply with national and international protocols and strategies to reduce the incidence of nosocomial infection. For example, the study of MRSA carriers as a predictor of pneumonia has a negative predictive value of 99.2%; however, this value does not reduce the number of infections or mortality [181]. *P. aeruginosa* is the leading cause of VAP in the ICU, and the risk increases with length of stay and airway manipulation, among other factors [177].

The most common surveillance programs include the search for MRSA, vancomycin-resistant Enterococci (VRE), carbapenemase-producing enterobacteria (CPE), *S. maltophilia*, *Burkholderia*, *Achromobacter*, *Candida auris* and azole-resistant *Candida parapsilopsis* to implement isolation measures and reduce cross-transmission to other patients. It is generally recommended to perform surveillance cultures on patients on admission to the ICU and at regular intervals to identify quickly carriers and adjust preventive measures [89]. Nowadays, in addition to conventional cultures, molecular biology techniques have been developed. They reduce the response time to hours, compared with classical techniques. Although the carrier state of resistant bacteria is important in making decisions about antibiotic use, the adjustment of the therapy should not be only based on this information and more risk factors must be considered. Moreover, a negative carrier culture should also not reduce the antibiotic spectrum when other risk factors exist [89].

Initial management of severe pneumonia and criteria for ICU admission

CAP is the third leading cause of death worldwide, and the leading cause of death due to infection. Its incidence varies from 1.2 cases/1,000 adults in Europe to 2.4 in the USA and is higher in people under 5 and over 65. The aetiology is unknown in more than half of cases, but identifying the causative microorganism is key to avoiding resistance to treatment. It is estimated that one third of patients are misdiagnosed. CAP is a serious disease, with 40-60% of patients requiring hospitalisation, and 30% of these patients' requiring admission to intensive care. Identifying this subgroup of patients is very important because they need specific tests and treatments. Delay in ICU admission is associated with increased mortality [1,182–185].

The most commonly isolated microorganism in CAP is *S. pneumoniae*, although a high proportion of CAP is of unknown origin. Viruses also play an important role in the development of CAP. However, some specific conditions are associated with other

microorganisms, such as exposure to air conditioning and *L. pneumophila* [182,186,187].

CAP is diagnosed following a radiological examination in a patient with symptoms and signs of a respiratory infection. The most common test performed is a chest X-ray. It has a sensitivity of 46-77% and can provide clues about the microorganisms involved. Computed tomography has a sensitivity of 100% and can provide information on complications, possible microorganisms involved and differential diagnosis (pulmonary embolism, pleural effusion, etc.). It exposes the patient to a high dose of radiation and its availability is limited. It is indicated in cases with poor clinical evolution, immunosuppressed patients, severe cases, and when differential diagnosis is needed. Finally, lung ultrasound has emerged in recent years as a powerful tool for diagnosing CAP. It is more sensitive than chest X-ray and can also detect complications. It requires appropriate medical training [150,183,188].

Tests for microbiological diagnosis are not recommended for outpatients. Patients requiring hospitalisation may require some tests, but patients with severe CAP need sputum and blood cultures and determination of urine antigen for *S. pneumoniae* and *L. pneumophila*. Molecular testing for detection of bacterial and viral pathogens may be indicated, and nasal screening for MRSA is recommended if being treated for MRSA. During epidemics of respiratory viruses, such as *influenza*, molecular detection of viruses is warranted [183,189].

Biomarkers, such as PCT and MR-proADM can provide information about the patient's prognosis. PCT must not be used as a guide to start antibiotic treatment [182]. MR-proADM have a greater accuracy than PCT for risk stratification of poor outcome and can be useful even in immunosuppressed patients [190]. Combination of MR-proADM with other biomarkers or clinical scores does not improve the MR-proADM´s accuracy [58].

CAP treatment must be effective, safe and respectful of the patient's microbiota. Possible regimens are summarised in **Table 6** [150,183]. A combination of a third-generation cephalosporin and a macrolide, such as ceftriaxone plus azithromycin, is strongly recommended [191–193]. In fact, this combination is associated with lower mortality than beta-lactam plus fluoroquinolone [194]. In some specific situations, other treatment regimens are recommended, such as levofloxacin for *L. pneumophila*, ertapenem for suspected anaerobes, or linezolid for suspected MRSA [182]. Another alternative is ceftaroline, a beta-lactam with a good activity against MRSA and with better clinical results than ceftriaxone [195]. In any case, time is of the essence for patients with severe CAP. The earlier the treatment is started, the better the outcomes, both in terms of hospital stay and mortality. Following the Survival Sepsis Campaign recommendations for the administration of antibiotics within the first hour of presentation in the emergency department, concerns were raised about the potential for overprescription of antibiotics, particularly given

Table 6. Initial treatment strategies for patients with community-acquired pneumonia. Adapted from Rodríguez-Leal CM et al and Candel FJ et al. [150,183].

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

COPD: chronic obstructive pulmonary disease; iv, intravenously, MDR: multidrug-resistant.
*Cefepime may be an alternative for some patients with suspected *P. aeruginosa.*

that the recommendation was based on a moderate level of evidence. As a result, the current recommendation is the administration of antibiotics within the first 3 hours in patients with sepsis [196]. However, in patients with septic shock, treatment must be started in the first hour [197].

As mentioned above, if a patient requires admission to an intensive care unit and that admission is delayed, the risk of death increases [198]. Prognostic scales such as the Pneumonia Severity Index (PSI, FINE), CRB-65, CURB-65 and Severity Community Acquired Pneumonia (SCAP, PS-CRUXO 80) give an acceptable estimate of the risk of death and are useful for deciding whether to manage the patient in the community or in hospital, but do not clearly identify the need for ICU admission. PSI underestimates risk in young patients, while CURB-65 overestimates risk in the elderly. SCAP can identify patients at risk of mechanical ventilation [182,183,197,199–204]. SMART-COP is a tool for predicting the need for intensive respiratory or vasopressor support in CAP, but its complexity of use and the existence of different cut-points have prevented its widespread use [183,205]. Nowadays, American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria are the preferred tool for deciding whether a patient requires ICU admission (**Table 7**) [183,186]. Early detection of severe pneumonia in the emergency department allows early initiation of antibiotic treatment, respiratory support if needed, and resuscitation with fluids and vasoactive drugs if required. This strategy results in fewer ICU admission, shorter times to ICU admission and lower mortality [183,206–208].

Influenza-associated invasive aspergillosis (IAPA) and COVID-19-associated invasive aspergillosis (CAPA). Diagnosis and treatment

IAPA and CAPA are opportunistic fungal infections caused by *Aspergillus* spp., that occur in patients with severe influenza infection or COVID-19, respectively. Viral infections disrupt the epithelial barrier. Subsequently, macrophage phagocytosis is altered, and conidial clearance is impaired. Finally, hyphae destruction by neutrophils is also reduced, allowing *Aspergillus* spp. to multiply easily. This situation can be aggravated by some drugs, such as oseltamivir, corticosteroids, and immunomodulators [209].

The incidence of IAPA and CAPA varies widely between regions and types of patients and is estimated to be around 10-20% in Europe. Awareness of the disease, the use of immunosuppressive drugs and a more severe clinical condition of patients, contribute to a higher incidence in recent years [209]. Vaccination against COVID-19 has led to an increase in the incidence of CAPA. This is due to a higher frequency of immunosuppressed patients with severe and mechanical ventilated COVID-19 infections and the presence of European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) host factors [210]. In contrast, influenza vaccination has led to a reduction in the incidence of IAPA but has not been associated with a decrease in its mortality [211].

Risk factors for IAPA include male sex, smoking habit, chronic lung disease, certain subtypes of H1N1 influenza virus, severe pneumonia requiring supportive care, use of corticosteroids prior to ICU admission, solid organ transplant recipients and haematological malignancy. In contrast, patients with CAPA are more likely to be older, have prolonged mechanical ventilation, use of certain drugs such as dexamethasone and tocilizumab, and have an analytical profile with elevated interleukin-6 and CD-4 lymphocyte depletion. Immunosuppressed patients are more common in IAPA (20-30%) than in CAPA (10%) [209,212,213].

Table 7. ATS/IDSA criteria to define severe CAP. Adapted from File TM *et al.* [186].

Major criteria	Minor Criteria
- Septic shock treated with vasopressors - Respiratory failure necessitating mechanical ventilation	- Respiratory rate ≥ 30 bpm - Confusion or disorientation - Hypothermia (temperature < 36°C) - Hypotension necessitating aggressive fluid resuscitation - Leukopenia (<4,000 cells/mm^3). - Thrombocytopenia (<100,000 platelets/mm^3). - Uremia: BUN ≥ 20 mg/dL. - Ratio PaO_2 to FiO_2 ≤ 250 - Multilobar (≥2) infiltrates

bpm: breath per minute, BUN: blood urea nitrogen level, PaO2: partial pressure of arterial oxygen, FiO_2: fraction of inspired oxygen.

Table 8. Definition of proven and probable influenza-associated invasive aspergillosis (IAPA) and COVID-19-associated invasive aspergillosis (CAPA). Adapted from Feys S et al, Verweij PE et al, and Koehler P et al. [209,214,216].

	IAPA	CAPA
Host factor	Influenza-like illness and positive influenza PCR or antigen And temporal relationship.	COVID-19 requiring intensive care and temporal relationship
Clinical factor	Radiological evidence of pulmonary or cavitary infiltrate	
Mycological evidence	**Proven** Lung biopsy showing invasive fungal elements and • *Aspergillus* growth on culture or • Positive *Aspergillus* PCR in tissue.	**Proven** (no clinical factor required) Necrotic ulcer (or other lesions evidenced in bronchoscopy) in the trachea or bronchi, with evidence of *Aspergillus* in tissue biopsy or *Aspergillus* recovered by culture, microscopy, histology or PCR obtained by sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process.
	Probable. A or B A: Pulmonary infiltrate and • Serum GM index > 0.5 or • BAL GM index ≥ 1.0 or • Positive BAL culture. B: Cavitating infiltrate not attributed to another cause and • Positive sputum or • Positive TA culture.	**Probable** Microscopic detection of fungal elements in BAL fluid, indicating a mould or Positive BAL culture or Serum GM/LFA index >0.5 or BAL GM/LFA index ≥ 1.0 or ≥ 2 positive *Aspergillus* PCR test in serum, plasma or whole blood or Single positive *Aspergillus* PCR in BAL (<36 cycles) or Single positive *Aspergillus* PCR in plasma, serum or whole blood and a single positive in BAL.

PCR: polymerase chain reaction. GM: galactomannan. BAL: bronchoalveolar lavage. TA: tracheal aspirate. LFA: lateral-flow assay.

In recent years, intensive efforts have been made to reach a consensus on diagnostic criteria for IAPA and CAPA [209,214–216]. They can be found in **Table 8**. In 2024, the Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU) published a new definition that is useful for unifying concepts in research but lacks applicability in clinical practice [215].

BAL is very important for diagnosis. Its sensitivity is around 50-60%, but it provides valuable information on species identification, antifungal susceptibility, anatomy of the bronchial tree and possible presence of tracheobronchitis, measurement of GM in BAL, which has a higher sensitivity than its determination in serum in this context, and finally, this procedure allows molecular techniques to be performed [217].

The clinical presentation of both diseases is difficult, and it is common for diagnosis to be made late, sometimes after the death of the patient. Two histological patterns have been described in necropsies [218].

- Non-impeded. It was observed in IAPA and tissue presented with a low degree of inflammation and a high degree of fungal invasion.
- Impeded. It was observed with both IAPA and CAPA. Lung tissue had a high degree of inflammation and a low degree of fungal invasion.

Other differences in the clinical presentation of IAPA and CAPA can be found in **Table 9**. IAPA tends to cause more epithelial damage and disruption of macrophage activity than CAPA. Oseltamivir also has a dual effect. When given early during influenza infection, it prevents the development of IAPA in mouse models; but when given late, it interferes with fungal recognition and promotes the development of IAPA [209,219,220].

Treatment can be made with either voriconazole or isavuconazole. The latter has a favourable profile for patients in ICU, as its metabolism is linear, and it has fewer interactions and side effects. In cases of resistance or intolerance to azoles, either liposomal amphotericin B or echinocandins, alone or in combination, can be used. The mortality rate of both entities is high, but it can be reduced with an early treatment. The duration of treatment must be individualised based on immunosuppression, clinical

Table 9. Clinical characteristics of influenza-associated invasive aspergillosis (IAPA) and COVID-19-associated invasive aspergillosis (CAPA). Adapted from Feys S et al [209].

	IAPA	CAPA
Presentation timing	Early since ICU admission, usually in first 48 hours	Late presentation, usually during second half of the first week in ICU
Angioinvasiveness	Very important	Less important
Serum GM positivity	50%	20-30%
Tracheobronchitis	30-50%	20-50%

ICU: intensive care unit. GM: galactomannan.

and radiological improvement. It is usually around 6 – 12 weeks. Other important considerations include optimising antiviral therapy, reducing or stopping immunosuppressive drugs as soon as possible, stopping antibiotic therapy if sterile cultures are obtained, and giving nebulised antifungals for tracheobronchitis forms [209,213]. Future possible treatment options may include fosmanogepix and olorofim for azole-resistant *Aspergillus*, and inhaled opelconazole (not active against *A. niger*) [221].

Finally, there is no evidence to recommend prophylaxis with either pocaconazole or isavuconazole [222,223]. Nebulised liposomal amphotericin B was associated with a lower incidence of CAPA in a retrospective study [224].

As previously described, opportunistic fungal infections have been reported in severe SARS-CoV-2 and influenza infections. With appropriate surveillance, a similar entity may be identified in patients with severe RSV infections in the future.

Current evidence in combined therapy in invasive fungal infections in critical care

Although the incidence of fungal pneumonia in Spanish ICUs does not yet exceed those caused by bacteria or viruses, patients arriving at the ICU are more complex and more susceptible to invasive fungal infections [225]. The epidemiological environment, local resistance to antifungals, limited therapeutic options for certain isolates, the occurrence of infections that are difficult to control, and the high mortality of IFI all make combination fungal therapy a feasible alternative [226].

Due to the eminent increase of *Candida spp*. resistant to antifungals (*C. auris*, fluconazole and voriconazole-resistant *C. parapsilopsis*), empirical treatment of IFI is usually guided using echinocandins or amphotericin B [227] until the details of sensitivity to other antifungals are known, given the severity of this type of infection and its complications [225,228]. For critically ill surgical patients with IFI, both appropriate source control and appropriate antifungal therapy were associated with reduced risk of 30-day mortality, and the protective effects of the two appropriate treatments are additive [229]. IFI due to *Aspergillus* spp., *Fusarium* spp., or Mucorales are also a topical issue mainly when it affects onco-haematological patients under immunosuppressive drugs that make them more susceptible to this type of infection. It is not possible to make a definitive recommendation for CAPA/IAPA patients, owing to the scarcity of published data [229,230]. Evidence supporting combination therapy as the first line of treatment in patients with IFI is weak, although it can be considered in critically ill patients with severe infection or when azole resistance is suspected. It is also important to consider factors that may affect the use of antifungals in addition to resistance [230]. For example, extracorporeal membrane oxygenation (ECMO) use may affect the pharmacokinetics of some antifungals or bioavailability in certain types of infection [231].

The current premises that support the use of combined antifungal treatment can be summarised as follows: broadening the spectrum of activity in empirical treatment in complex situations, greater fungicidal activity (synergistic effect), delaying or preventing the emergence of resistance, reducing doses and minimising toxicity, treatment of infections with the presence of biofilm, complex localised infections with difficult penetration of antifungal treatment, breakthrough fungal infections and the treatment of mixed fungal infections. On the contrary, these combinations may have drawbacks such as: drug interactions, lack of evidence for the use of some combinations in real life, increased toxicity, selection of resistant fungi, incompatibility with increased side effects and the cost generated [232–234].

New evidence in the diagnosis and follow-up of fungal pneumonia

In order to cover an IFI, a diagnostic suspicion must first be raised. Among the main causes of fungal pneumonia, we can find: *Aspergillus* spp., Mucorales,

Lomentospora prolificans, *Fusarium solani*, *Scedosporium spp*., other cryptic *Aspergillus* or even in severe cases combinations of them. The type of patient who can present IFI is no longer focused solely on onco-haematological patients. It can also affect patients being treated with other biological immunosuppressive drugs, corticosteroids or patients with previous infections due to viruses (like SARS-CoV-2 or influenza) or bacteria [235,236]. Pneumonia caused by fungi should be present in the arsenal of suspicions in patients who meet these risk factors in addition to classic immunosuppression criteria. Annually, over 2,113,000 people develop invasive aspergillosis in the context of COPD, intensive care, lung cancer, or haematological malignancy, with a crude annual mortality of 1,801,000 (85.2%) [226].

Suspicion of IFI should not be considered as a last resort, in patients who have been hospitalised for several days and with broad-spectrum coverage. It should be considered in the early days (ideally within the first five days) of the illness, particularly in severe pneumonia [237]. Empirical coverage of IFI could also be considered until microbiological results are obtained in patients with radiological images compatible with pneumonia due to fungi with other concomitant risk factors [238], since early targeted treatment of an IFI potentially increases the chances of success [239]. Currently, microbiology laboratories are equipped with tools for the early detection of IFI such as conventional microscopy (calcofluor), PCR assays and other biomarkers (like β-D-glucan or galactomannan), tests based on detection of fungal antigens released in their invasive stages which an earlier result than the conventional culture [240]. However, in many cases these tests may not be conclusive due to the type of sample or other characteristics of the causal microorganism, making empirical treatment also of great value when it is suspected [241].

However, despite the inclusion of rapid techniques applied to the diagnosis of IFI, there are still great future challenges, such as the detection of resistance (for example azole resistance in *Aspergillus spp*.), growth of colonizing fungi in conventional cultures with difficult assessment, and the absence of multiplex platforms based on PCR marketed to detect main causes of IFI [238,240,241].

Express update in antimicrobial therapy

Delafloxacin

Delafloxacin is presented in the therapeutic arsenal as a new fluoroquinolone with a different anionic chemical structure from the rest of those on the market. This anionic structure allows greater penetrability in acid environments, with good antibiofilm activity, and the ability to inhibit topoisomerases II and IV, achieving greater spectrum and potency on both gram-positive and gram-negative bacteria than previous quinolones. It also presents a greater antibiotic spectrum, with less capacity for resistance selection and a more favourable safety profile than the rest of fluoroquinolones. It presents activity against gram positive bacteria (including *S. pneumoniae* resistant to penicillins, MRSA, coagulase negative *Staphylococcus*, even those gram-positive resistant to other quinolones). However, it does not present activity against *E. faecium*. It shows a broad spectrum against enterobacterales including *P. aeruginosa*, atypical bacteria (*Mycoplasma* spp., *Legionella pneumophyla*, *Chlamydia* spp.), and anaerobes. It does not present activity against ESBL-producing enterobacteria or carbapenemases with resistance to other quinolones [242–244]. It allows oral or intravenous administration, with time-dependent bactericidal activity and high penetration into lung tissue [244]. In 2024, the National Health System included indication of delafloxacin for CAP subject to special situations. Changing aetiology and increasing antimicrobial resistance have made CAP more challenging to treat empirically, particularly among patients with chronic comorbid diseases [245]. Delafloxacin has demonstrated non-inferiority to moxifloxacin in a phase III clinical trial but was shown to be superior to moxifloxacin at early clinical response in CAP patients who also have COPD or asthma as a comorbidity, and in CAP patients who have more severe illness [244]. All these properties make delafloxacin an alternative available in the therapeutic arsenal for CAP in special situations to avoid excessive use of other antibiotics [246].

Ceftaroline

Ceftaroline is a broad-spectrum, fifth-generation cephalosporin specifically targeted for the treatment of MRSA. Its structure presents modifications that allow it to evade resistances that make other cephalosporins not active for MRSA. It is worth highlighting its 1.3-thiazole group that confers anti-MRSA activity, and a 1,2,4-thiadiazole group that confers penetration and anti GNB activity [247]. It is also endowed with a phosphonic group present in the prodrug that increases its solubility in the plasma medium. It has low binding to plasma proteins, with mainly renal elimination and does not require dose adjustment in hepatic failure or in advanced age [247,248]. Its antibacterial activity allows coverage of *S. aureus* sensitive or resistant to methicillin, vancomycin-intermediate/resistant *S. aureus*, *S. pyogenes*, *S. pneumoniae*, S. *anginosus group* and GNB such as *E. coli*, *K. pneumonie/oxytoca*, *H. influenzae/parainfluenzae*, *M. morganii*

and *Moraxella catarrhalis* [248]. In the latest publications it has been shown that ceftaroline can be an alternative in the treatment of conventional severe CAP and VAP, reducing the value of hospital mortality in seriously ill patients[249–251]. Ceftaroline could be used also in empirical treatment when MRS or penicillinase *S. pneumoniae* is suspected; or in patients with post viral CAP [252,253]. In conclusion, ceftaroline stands out from other cephalosporins due to its activity against MRSA. However, it is important to highlight its potent anti-pneumococcal activity, which has demonstrated an early clinical response. Therefore, it should not be restricted exclusively to infections with a resistance profile.

Ceftobiprole

Ceftobiprole is an antibiotic belonging to the fifth generation cephalosporins. It has anti-MRSA activity, penicillin-resistant *S. pneumoniae*, and activity against *P. aeruginosa* like ceftazidime [254]. Approved by AEMPS for use in CAP and HAP (excluded VAP). Recent studies show that ceftobiprole does not display inferiority compared to ceftriaxone (combined or not with linezolid) in the treatment of CAP and HAP [255,256]. Furthermore, alternative studies show that ceftobiprole may be an available alternative in the treatment of complicated bacteraemia caused by methicillin sensitive *S. aureus* compared to other available alternatives such as daptomycin or vancomycin [257–261]. There is synergistic effect in combination with other drugs for the treatment of complicated infections, such as endocarditis, bone and joint infections, or in patients undergoing ECMO, caused by MRSA or *E. faecalis*. All these studies show that ceftobiprole could be a therapeutic alternative available both as monotherapy and in combination for the treatment of complicated infections apart from CAP and VAP [259–261] .

Cefepime-enmetazobactam

Cefepime-enmetazobactam emerges as a new combination of a fourth-generation cephalosporin (Cefepime) with a broad-spectrum beta-lactamase inhibitor (Enmetazobactam). The methyl group of the triazole ring of enmetazobactam allows many classical and non-classical hydrogen bonding interactions that are not observed in other widely known inhibitors such as tazobactam [262]. This combination presents activity against ESBL-producing enterobacterales (specifically class A such as CTX-M, TEM or SHV), AmpC and OXA-48 like type carbapenemasas [263,264]. Since enmetazobactam restores the activity of cefepime against ESBL-producing pathogens and stabilizes the activity of cefepime against AmpC and OXA-48-producing pathogens, this constitutes a promising option for saving carbapenems. Furthermore, enmetazobactam has a zwitterion-type structure, which increases its penetration into the periplasmic space of bacteria [265].

However, despite these developments, this combination does not provide additional coverage for *P. aeruginosa* compared to Cefepime in monotherapy in susceptible isolates [266]. The FDA has approved the use of this antibiotic for the management of complicated urinary tract infections (including pyelonephritis), HAP and VAP, with or without concurrent bacteraemia [267]. Regarding its pharmacokinetic and pharmacodynamic behaviour, it presents pharmacodynamic optimization parameters similar to those of the rest of beta-lactams (T>MIC) but with a tissue diffusion ratio higher than other penicillins with penicillinases (similar to combinations of carbapenem with inhibitor) in modelling healthy adults and in murine pneumonia models [265,268]. It is not a therapeutic alternative for the treatment of enterobacterales producing KPC carbapenemase, MBL, *P. aeruginosa* MDR or *Acinetobacter baumanii* MDR (although it has a partial effect on *A. baumanii* resistant to carbapenems) [262,266].

Ceftolozane-tazobactam

Ceftolozane-tazobactam is an antibiotic with an excellent activity against *P. aeruginosa* (PAER). It is a robust antibiotic against the resistance mechanisms of this bacterium. Tazobactam is a beta-lactamase inhibitor, which is not needed for antipseudomonal activity, but extends the activity of ceftolozane against other bacteria with beta-lactamases [269]. Given that HAP is the most common nosocomial infection, this antibiotic plays an important role in its treatment [270]. EPINE data show that PAER is commonly isolated in community-acquired infections requiring hospitalisation, with a prevalence of carbapenem resistant of 17%. It is more prevalent in nosocomial infections, causing 26% of VAPs with an associated mortality rate of 33% [271]. ENVIN-UCI-2023 data show similar results, perhaps with a higher incidence of resistance due to its different methodology [87].

HAP-VAP is an infection with inoculum effect. The high bacterial load and biofilm formation affect antibiotic activity, especially with older beta-lactam antibiotics, such as ceftazidime and cefepime. These conditions can lead to clinical failure and development of resistance during antibiotic therapy [272,273]. Ceftolozane-tazobactam has a very favourable pharmacokinetic and pharmacokinetic profile. It is less affected by inoculum effect because its minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) are very close. This property prevents resistant mutants [274,275]. This gap between MIC and MBC is known as the mutant

selection window, and the wider it is, the more likely is that resistant mutants will develop [276]. This advantage of ceftolozane-tazobactam translates clinically into lower mortality in VAP compared to meropenem [277,278]. These results have been replicated in other settings, such as neutropenic patients [279]. Moreover, the earlier in the course of infection this drug is started, the more effective is [280]. For these reasons, a recent study suggests that ceftolozane-tazobactam must be a first-line antibiotic for infections caused by PAER [281]. Finally, current guidelines recommend ceftolozane-tazobactam for pseudomonal infections [282–284].

Ceftazidime-avibactam

Ceftazidime-avibactam is an antibiotic that has been approved since 2015. It is an appropriate antibiotic for the treatment of HAP-VAP due to its appropriate spectrum, good penetration into the lung parenchyma and favourable clinical results in clinical trials and observational studies [285–287]. Avibactam is a beta-lactamase inhibitor with activity against beta-lactamase classes A (including ESBLs and KPC-type carbapenemases), C (AmpC) and some subtypes of type D (OXA-48). It has no activity against metallo-β-lactamases (type B) [288].

As mentioned above, resistant bacteria are common in patients with HAP-VAP. PAER and *K. pneumoniae* are the most common microorganisms isolated in HAP-VAP, often with production of ESBLs or carbapenemases [87,289]. Although there is considerable heterogeneity between Spanish regions, the most frequently isolated carbapenemase type is OXA-48, followed by KPC [290]. As a result, ceftazidime-avibactam has in vitro activity against 83% of PAER isolates in 2022, only comparable to susceptibility of amikacin, tobramycin and colistin [291]. Pharmacokinetic properties are also favourable, with a good correlation (20-30%) of antibiotic concentrations between serum and epithelial alveolar surface [292]. This concentration is enough to achieve a bactericidal effect [293–295]. These characteristics correspond to good clinical results with little influence from the inoculum effect and high cure rates in the case of associated bacteraemia [296–299]. Moreover, ceftazidime-avibactam has no activity against anaerobes. This condition has been associated with lower mortality in critically ill patients [300]. As a result, ceftazidime-avibactam is recommended as empirical treatment in specific situations and is now the sixth most commonly used antibiotic in HAP-VAP [87,150,151].

Aztreonam-avibacta

The combination of aztreonam with avibactam is a therapeutic alternative for MBL-producing GNB, although this combination has been shown to be less effective against some isolates such as *P. aeruginosa* [301]. However, this combination is also stable against Class A beta-lactamases (KPC), AmpC, Class D (OXA-48 like) and ESBL. It presents a potential indication in HAP/VAP; complicated intra-abdominal infection (cIAI) associated with an antimicrobial against anaerobic bacteria such as metronidazole; complicated urinary tract infection (cUTI) and blood/sistemic infectios (BSI). Since the aztreonam/avibactam combination is still in clinical trials (currently mostly phase 3), various approaches using ceftazidime/avibactam (CAZ/AVI) with aztreonam (AZT) have been employed in microbiology laboratories to evaluate the *in vitro* synergy of this drug combination against MBL-producing GNB [302]. Unified standardized methods to evaluate this synergy *in vitro* in laboratories have yet to be well established. The PANNUCI algorithm recommends the combination of CAZ/AVI + AZT or cefiderocol as a targeted therapy for MBL-producing GNB HAP/VAP. Particularly, for MBL-producing *P. aeruginosa*, cefiderocol is the first choice, better than the CAZ/AVI + AZT combination. For carbapenem-resistant *A. baumannii* (CRAB) or MBL-producers, the combination of CAZ/AVI + AZT is not an available alternative. In CRAB-MBL-producer infections, cefiderocol combined with other active antibiotic (tigecycline, eravacycline, fosfomycin or aminoglycosides) can be consider as the first treatment option [301,303]. IDSA 2024 guidelines recommends combination of CAZ/AVI + AZT as treatment of HAP/VAP by *S. maltophilia*, or two of the following agents: TMP/SMX, levofloxacin, minocycline or cefiderocol [304].

Cefiderocol

Cefiderocol is a treatment option for HAP that has demonstrated non-inferiority compared to meropenem in the APEKS-NP trial. It has a good profile against multi-resistant gram-negative bacteria [305]. Since the publication of this study, several publications of real-world data from different countries have shown its therapeutic efficacy and safety. It has a success rate of about 80% when used as first-line therapy, but this drops to 45-60% when used as second-line therapy or against *A. baumanii* [306–311]. For this microorganism, it is important to optimise administration to avoid treatment failure [312]. Patients treated with ECMO do not require dose adjustment [313]. An active area of research is how to optimise dosing to reduce costs [314]. Finally, current IDSA recommendations suggests the use of cefiderocol as first-line therapy for infections caused by gram-negative bacteria with carbapenemase type NDM and as second-line therapy in combination with ampicillin/sulbactam for carbapenem-resistant *Acinetobacter* [315].

Imipenem-relebactam

Imipenem is a bactericidal antibiotic with good activity against gram-negative bacteria, including those that produce ESBL (Extended-Spectrum-β-Lactamase), gram-positive bacteria, and anaerobes. It inhibits mural cell synthesis by inhibiting penicillin-binding-proteins (PBP). Relebactam is a new beta-lactamase inhibitor with activity against type A (including ESBL and KPC) and C. It is inactive against metalo-β-lactamases (MBL). It increases imipenem activity against enterobacteria and PAER fivefold and restores activity in two out of three cases of carbapenemase producing PAER isolates. Neither imipenem nor relebactam are affected by efflux pumps. Moreover, the total dose of imipenem required with this combination is lower than with imipenem alone, and it has a better activity against gram-positive bacteria than meropenem. Also, it has a low risk of resistance development [316]. Finally, it has high pulmonary diffusion. Its exposure in epithelial lining fluid relative to plasma was 54% for relebactam and 55% for imipenem, after adjusting for protein binding [317].

Clinical efficacy was demonstrated in the RESTORE-IMI 1 and RESTORE-IMI 2 trials against the combination of imipenem and colistin, and piperacillin-tazobactam, respectively. It was tested in intra-abdominal infections, urinary tract infections and HAP-VAP. Imipenem-relebactam also showed a good safety profile with no neurological toxicity and less renal toxicity [318–320]. Therefore, imipenem-relebactam is indicated for HAP-VAP with or without bacteraemia, intra-abdominal and urinary tract infections. The recommended duration of treatment is seven to fourteen days for HAP-VAP and five to ten days for the other two indications. The usual dose is 500 mg of imipenem in combination (one vial) given as a 30-minute infusion every six hours, but dose adjustment is required in patients with renal failure [316].

Meropenem-vaborbactam

Vaborbactam is a beta-lactamase inhibitor with activity against class A (including KPC carbapenemases) and C beta-lactamases. It is not hydrolysed by beta-lactamases and has potent and specific activity against KPC. It has no activity against class B and D carbapenemases. As a result, it restores the activity of meropenem against beta-lactamase A or C producing bacteria [321–323]. Carbapenemase-producing bacteria are a global problem, although Europe has a lower prevalence than other continents such as Asia, Latin America and Africa [324]. In Spain, the prevalence of carbapenemase-producing bacteria is heterogeneous, and the frequency of each class of beta-lactamase varies between regions. Moreover, the local epidemiology of each hospital and ICU service is important in making treatment decisions [325]. For infections caused by carbapenemase-producing bacteria, an early and appropriate treatment reduces attributable mortality [326]. Susceptibility of KPC-producing bacteria to meropenem-vaborbactam, such as *Enterobacterales*, *Achromobacter* and *Burkhorderia*, is over 90 percent, and in some cases almost all isolates were susceptible [321,325]. It also has potent in vitro activity against isolates resistant to ceftazidime-avibactam. A mutant variant of *ompK36* in KPC-producing *K. pneumoniae* increases the MIC of meropenem-vaborbactam [327]. From a pharmacokinetic point of view, it also has excellent penetration into the lung parenchyma [159,321]. Its clinical efficacy was demonstrated in the TANGO II trial, which was stopped early due to the good clinical results of meropenem-vaborbactam compared to the best available therapy [328]. However, when used as rescue therapy after failure of a previous antibiotic regimen, clinical outcomes are worse. This suggests that meropenem-vaborbactam should be started earlier in appropriate patients [329,330]. Current Spanish guidelines position meropenem-vaborbactam as a recommended therapy against KPC-producing *Enterobacterales*, with the same level of evidence as ceftazidime-avibactam, although IDSA-guidelines favour meropenem-vaborbactam over ceftazidime-avibactam [282,283]. Both guidelines suggest that the use of cefiderocol should be reserved for specific cases.

Conclusions

With all this knowledge reviewed and updated, and planning content of maximum interest for upcoming World Pneumonia Day commemorations, it is difficult to refrain from making some final comments on personalised medicine and the role of artificial intelligence (AI) in the management of pneumonia. The future of pneumonia is heading towards a more personalised approach, where diagnosis and treatment will be tailored to the individual characteristics of each patient. Quite possibly, if not already happening, AI will facilitate the integration of genomic, clinical, microbiological, epidemiological, and environmental data to achieve this goal. Telemedicine, driven by improvements in interconnectivity and AI, will enable more effective remote monitoring of pneumonia patients, especially those with chronic diseases or in remote or rural areas. This will improve access to care and enable early intervention in case of complications [331].

Clearly, it can help achieve improved diagnostics, for example in advanced image analysis. AI can analyse X-rays and computed tomography scans more accurately than the human eye, detecting subtle patterns

that indicate pneumonia (or pneumonitis) and differentiating between bacterial, viral or fungal causes alongside other biomarkers and microbiological studies. This will enable faster and more accurate diagnosis, especially in resource-limited settings. In addition, it will play a key role in early detection, particularly by enabling AI algorithms to analyse clinical data (symptoms, vital signs, laboratory tests) and identify patients at high risk of developing pneumonia, experiencing complications, or progressing to a worse prognosis, thereby allowing early intervention. AI can speed up the analysis of biological samples, such as sputum or bronchoalveolar fluid, identifying pneumonia-causing pathogens and their resistance to antibiotics more quickly [332].

Personalised treatment, supported by AI, can improve prediction of the severity of pneumonia and the risk of complications, helping clinicians to decide the level of care needed (outpatient, inpatient, ICU). Similarly, it can optimise antibiotic treatment by analysing clinical and microbiological data and recommending the most effective antibiotic for each patient, minimising the risk of resistance, side effects and drug interactions. In addition, it can facilitate more continuous monitoring, through wearable devices and smart sensors that could collect real-time data on lung function and other vital parameters, enabling successive monitoring of treatment response and early detection of complications [333].

However, several challenges and considerations about the role of AI in pneumonia cannot be neglected, including, as in many other infectious processes and syndromes, issues of data quality, clinical validation, ethics and privacy, integration into clinical practice, and accountability [331–333].

AI depends on high-quality data to function properly. Ensuring the accuracy and completeness of clinical and imaging data is crucial. AI algorithms in the management of pneumonia will need to be rigorously validated in clinical studies to demonstrate efficacy and safety before widespread implementation. Of course, it is critical to address the ethical and privacy issues related to the use of AI in healthcare, ensuring the confidentiality of patient data. And AI will also need to be seamlessly integrated into existing clinical workflows, facilitating its use by clinicians and other healthcare professionals. Furthermore, responsibilities for the use of AI will need to be clearly defined, establishing clear protocols for clinical decision-making [331,333].

AI therefore has the potential to transform the management of pneumonia, improving diagnosis, treatment, and health outcomes at the population level and for individual patients. However, it will be critical to address ethical challenges and considerations to ensure its responsible and effective implementation.

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