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XIII Updating Course of Antimicrobials and Infectious Diseases 2023

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Introduction

Francisco Javier Candel

Introduction to XIII Updating Course of Antimicrobials and Infectious Diseases

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22	Argentina
19	Peru
13	Chile
11	Italy
10	Ecuador
7	Mexico
7	Costa Rica
6	United Kingdom
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5	Paraguay
5	United States
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4	Bolivia
2	Brazil
1	El Salvador
1	Guatemala
1	Netherlands

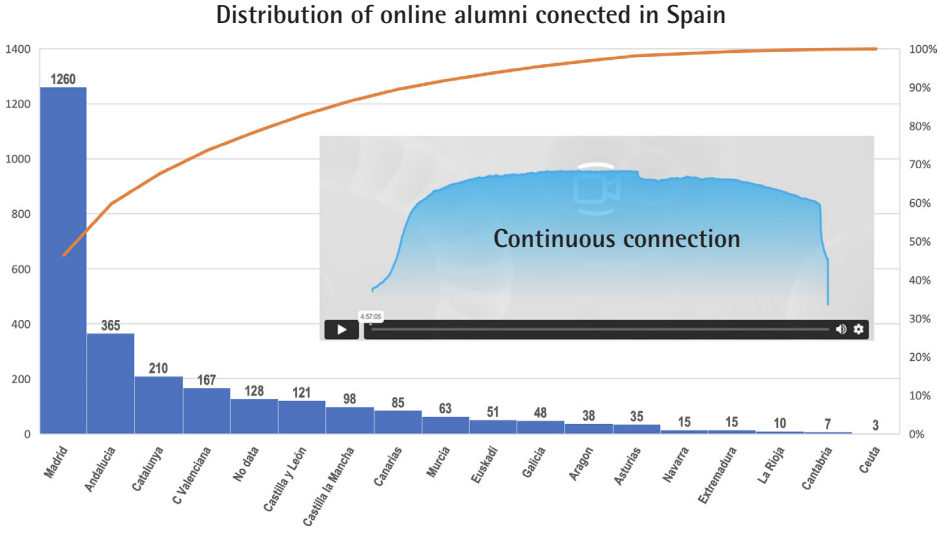

Figure 1 | **Distribution of "XIII Infeclinico" online alumni and their origin.**

Last february, the XIII Updating Course of Antimicrobials and Infectious Diseases was held at the Hospital Clínico San Carlos in Madrid. It is a scientific activity accredited by the Community of Madrid (Commission for Continuing Education of Health Professions at the Community of Madrid, file number 07-AFOC-00085.6/2023, 1.3 credits) and endorsed by the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), the Spanish Society of Chemotherapy (SEQ) and the Madrid Society of Clinical Microbiology (SMMC). This year, the course was mix edited presential-online and reached 177 asistants and 2751 continuous connections from Spain and other european or american countries (Figure 1). The audience consisted of multidisciplinar proffesionals of all specialties related to infection, the teachers made an update of the most relevant aspects on bacteriology, mycology and virology.

Current issue of the magazine includes summaries of the lectures given in the presential course. It also includes the questionnaire with the evaluations made by the students and a sheet of correct answers to being able to contrast the results.

The supplement is divided into five headings.The first section, entitled "*Bacteremia and sepsis*" included topics such as the management of streptococcal bacteremia or the workflow of the microbiology laboratory in sepsis. The second one dealt with *respiratory infection*. It included an approach to the management of nosocomial pneumonia and the risk of SARS-COV-2 infection and its management in the solid organ recipient. The third section addressed the *main emerging infections* at the beginning of 2022, such as the monkeypox outbreak or invasive Streptococcus spp group A (GAS) infection. In the *clinical approach* round table, a practical vision of the management of skin and soft tissue infections was presented, taking into account the continuity of care, assessing the role of new antimicrobials against resistant gram-positive bacteria. A comparative analysis was also made between the different American, European and Spanish guidelines in the treatment of resistant gram-negative microorganisms. Finally, infection in patients undergoing CAR-T therapies was reviewed. In the last table of *trends in infectious diseases*, the present and future of resistance in *Pseudomonas aeruginosa*, the new antifungal treatment pipeline and a selection of outstanding articles in infectious diseases and clinical microbiology in the last two years were analyzed. I hope you enjoy reading it.

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Marino Blanes Juliá

Enterococcus spp. and *Streptococcus* spp. bloodstream infections: epidemiology and therapeutic approach

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ABSTRACT

Streptococcus spp. and *Enterococcus* spp. are frequent etiologies of bloodstream infection and endocarditis. In recent years, the incidence of *Enterococcus* spp. has been increasing, especially with nosocomial involvement, and with a high mortality rate. In this entity, the risk of endocarditis and its relationship with colorectal neoplastic pathology remains to be clarified, in order to establish indications for echocardiography and colonoscopy. In the case of *Streptococcus* spp., the risk of endocarditis depends on the species and the mortality rates are usually lower. Finally, in recent years, the treatment of endocarditis has been directed towards oral consolidation regimens and new long-term antibiotic treatments.

Keywords: Bacteremia, bloodstream infection, *Enterococcus faecalis*, *Streptococcus* spp. epidemiology, endocarditis

INTRODUCTION

Streptococcus spp. and *Enterococcus* spp. are a group of Gram-positive cocci that typically grow in chains or pairs. Both groups are commensal from human mucosa of the respiratory or the intestinal tract.

The genus *Streptococcus* spp. includes a wide variety of species that have been classically divided into six groups based on phylogenetic relationships. Currently, they are usually identified and classified by MALDI-TOF technique which has a high sensitivity and very low false positive rate.

The genus *Enterococcus* spp. was separated from *Streptococcus* in 1986.

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EPIDEMIOLOGY OF BACTEREMIA AND INFECTIOUS ENDOCARDITIS

Enterococcus spp. bacteremia

Enterococcus spp. are the causative microorganism of 10% of all bloodstream infections (BSI) and constitute the third cause of Gram-positive BSI in Europe with a incidence of 7-19/100.000 person-years [1], after *E. coli* and *S. aureus*. This pathogen is more related to healthcare acquisition and it frequently affects elderly, fragile and immunocompromised patients [2].

More than two thirds of this bacteremia are caused *by E. faecalis* while *E. faecium* causes less than one third of them. The focus of the BSI is different depending of the aetiology: in *E. faecalis* a urinary infection is the most usual, while in *E. faecium* it is an abdominal or unknow focus, with more relationship with nosocomial infections [2]. Furthermore, endocarditis is also more frequent in *E. faecalis* bacteremia (90% of enterococcal endocarditis are due to *E. faecalis*) [3,4].

It is also important to notice the growing detection of vancomycin-resistant enterococci, much more frequent in *E. faecium*, especially among nosocomial infections [5].

In a percentage variating from 5-20%, enterococcal bacteremia can be associated to infectious endocarditis (IE), especially among older patients [2,4]. In recent years, these pathogens are becoming more common, and in last published series enterococcal IE is the third main cause of IE (15-30%) [2]. The indications of echocardiography in these patients have not been clarified at present. Scores such as NOVA and DENOVA scores which can predict the risk of endocarditis have been developed, and therefore, the indication of echocardiography [3]. However, further validations are needed to standardize these scores.

The mortality of these BSI and IE is around 20% [6], strongly influenced by risk factors of the patients. It is higher among *E. faecium* bacteremia, especially in vancomycin-resistant enterococci.

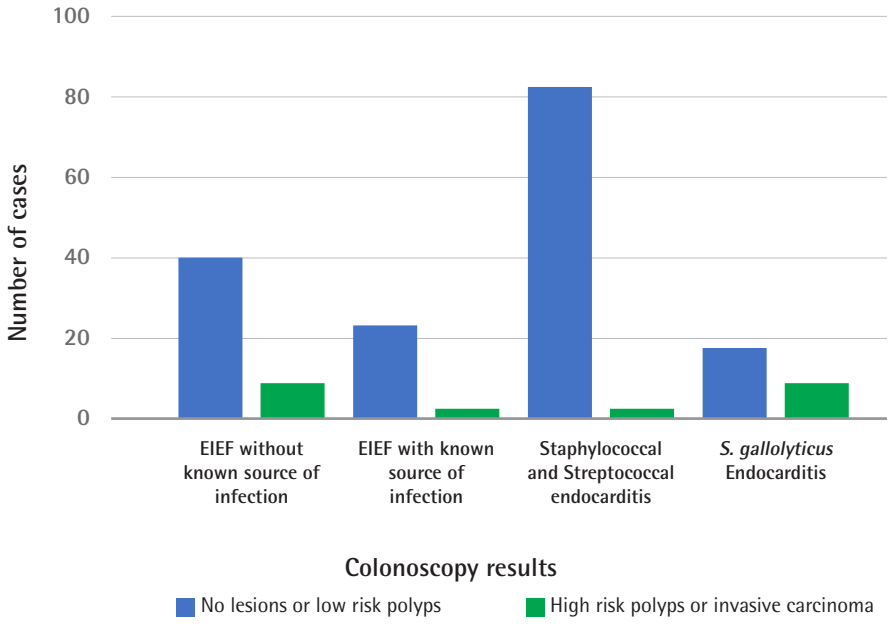

Figure 1 | **Data from retrospective study in Hospital Universitario y Politécnico La Fe, Valencia, 2010-2022**

Streptococcus spp. bacteremia

Streptococcus spp. group is also a frequent microorganism involved in BSI. Bacteremia can be associated to IE in a different proportion depending on the specie, from 0-48% with an average of 7,1% [7]. IE is more probable in *S. mutans, S. gordonii, S. sanguinis* and *S. gallolyticus* (with a prevalence of more than 30%) and much less probable in *S. pyogenes* and *S. pneumoniae*. Recently, with the use of new diagnosis techniques for classification of streptococci, *S. tigurinus* has been described as a new species which has also frequently been related with IE [8].

It is also important to notice that bacteremia for *S. anginosus* is mostly related to abscesses and it is rarely a contaminant when isolated from blood cultures [9]. For this reason, if *S. anginosus* is detected in blood cultures, antibiotics for anaerobic bacteria should be considered.

The mortality rate of streptococcal BSI and IE depends also on the specie between 5-20% [6,7].

RISK OF COLORRECTAL PATHOLOGY

In the pathogenesis of BSI, the need to look for the source exists. It is mostly related to with intravenous catheters, but in some species, such as *S. gallolyticus* or *E. faecalis*, it can be related to colorectal lesions.

In the case of *S. gallolyticus,* this relationship was first described in 1974 and it has been widely studied [10]. For this reason, current American and European guidelines of IE indicate systematically colonoscopies when IE by this microorganism is diagnosed.

In the case of *E. faecalis,* this relationship has not been established clearly and doubts remain of when to indicate colonoscopies in these patients. In some recent studies it has been suggested that patients with an unknown focus of the infection have a higher probability of colorectal lesions than patients with known focus, most commonly urinary focus [11,12].

However, there is a need for further prospective studies to establish general recommendations.

TREATMENT

The initial management of BSI and IE must be intravenous. However, there are recent studies that support early switching to oral antibiotics with non-inferior results [13,14].

In *Streptococcus* spp. bacteremia there is a retrospective study which pleads for a short period of intravenous antibiotics (3-5 days) and early switching to oral antibiotics. However, the streptococci were mostly *S. pneumoniae* and pyogenic streptococci and bacteremia were non-complicated, so these results need further studies to be generalised.

On the other hand, the antibiotic management of IE has always been based on long periods of intravenous antibiotics (6 weeks). In the last few years, it has been suggested that IE could be managed with initial intravenous antibiotics followed by oral antibiotics if the evolution has been favourable. In this regard, the POET trial was first published in 2022 [13] with no difference in long follow-up with oral or intravenous antibiotics in IE patients.

Moreover, due to the increasing age of the patients who are being diagnosed with IE in the last few years, it is becoming more frequent for patients not to be candidates for surgical intervention, despite surgery is indicated. For this reason, long-term antibiotics have been proposed and some new long-action antibiotics are gaining importance in this matter. These antibiotics, dalbavancin and oritavancin have been studied mostly in consolidation of IE with good results. The doses have not yet been fully clarified and differ between different trials [15,16].

HIGHLIGHT POINTS

- IE prevalence among streptococcal bacteremia depends on the streptococci specie
- *E. faecalis* bacteremia is frequently associated with IE, it is necessary to establish clear indications of which patients should undergo an echocardiography
- *E. faecalis* IE seems to be associated with colorectal pathology, but less frequently than *S. gallolyticus*. It remains unclear when to indicate a colonoscopy and it may depend on the existence of a source of infection
- Treatment of IE is changing and there are recent studies which defend oral consolidation therapy
- The rise in average age of IE patients does not allow surgery in many cases, which forces them into a long-term antibiotic period. New long-action antibiotics will be a good option to the ambulatory management of these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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The microbiology of sepsis is more than the application of new technologies in diagnosis

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ABSTRACT

Adequate and rapid microbiological diagnosis of sepsis is essential for correct treatment, having a direct impact on patient prognosis. Clinical Microbiology Services must adapt fast circuits that allow prioritizing and individualizing the diagnosis of these patients. The measures adopted should not be based solely on the incorporation of new technologies but, to a large extent, on ensuring accurately collection and processing of samples, avoiding unnecessary losses of time in processing and ensuring that the information derived from this process adequately reaches the prescribing physician.

Keywords: Sepsis, Sepsis Code, Sepsis microbiological diagnosis

INTRODUCTION

According to the World Health Organization, sepsis is currently considered a global health priority and the leading infectious cause of death**.** Despite the lack of a single definition, adequate epidemiological records and underestimation of the data available, a study published in *The Lancet* in January 2020 estimated the global burden of sepsis in 2017 to be 48.9 million incident cases and 11.0 million deaths worldwide [1].

There are two fundamental aspects to consider in sepsis: anyone can suffer an infection and almost any infection can lead to sepsis. When, this occurs every second counts (https://www.cdc.gov/patientsafety/features/get-ahead-of-sepsis.html), since the associated mortality must be fought with a diagnosis and proper management within the first hours. Currently, application of the measures recommended by the Surviving Sepsis Campaign reduces morbidity and mortality to around 25% [2]. In Spain, the key points of this intervention are focused on the Sepsis Code, implemented in Catalonia and other autonomous communities since 2015. The main goal of this code is the early detection of patients at risk and the rapid application of a set of measures to establish an etiological diagnosis, monitoring the different organs susceptible to failure, and starting empirical antibiotic treatment, resuscitation with fluids and life support.

Regarding microbiological diagnosis, although these recommendations are individually adapted in each centre, it is recommended to take at least 2-3 sets of blood cultures (BC) early, preferably before starting antimicrobial treatment, in addition to collecting other clinical samples of the probable source of infection. Rapid diagnostic laboratory techniques must be applied to these samples to report preliminary results quickly. Therefore, the microbiology laboratory must use all the available resources to help differentiate whether a patient really has sepsis or another condition which could appear with the same non-specific symptoms. In the case of considering that it is a septic condition, the source of infection must be established, as well as determination of the causative agents and how to direct the treatment adequately, all within the shortest possible time (ideally in less than 24h from symptom onset, if possible). Several studies have reported that the initial antibiotic therapy in sepsis needs to be not only timely but also appropriate [3]. Despite the publication of therapeutic guidelines and protocols, around 1 in 5 patients with bloodstream infection (BSI) in the United States receive susceptibility-discordant empirical antibiotic therapy [4] and this number may be even higher if the choice of the drug, the dose and method of administration are considered.

According to Brigitte Lamy and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Bloodstream Infections, Endocarditis and Sepsis (ESGBIES) [5], to achieve progress in bloodstream infections, aetiological diagnoses should be based on a bundle approach. This approach is based on optimizing pre-analytical measures

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(skin preparation, volume of blood sampled, sample transportation to laboratory and rapid start of incubation), improving the analytical process (fast processing of positive flagged bottles and use of quick identification and antimicrobial susceptibility testing methods) and post-analytical actions, especially close collaboration with the sepsis team. By combining all of these actions, the diagnosis of sepsis can be significantly improved.

PRE-ANALYTICAL MEASURES

Diagnostic performance can be improved by considering some essential pre-analytical aspects. First, in addition to the BC, it is a priority to process other biological samples to determine the source of the infection. Furthermore, if possible, these samples must be collected before administering the first dose of the antimicrobial, as long as this does not delay the start of treatment by more than 45 minutes, since obtaining BCs during antibiotic therapy is associated with significant hindrance of pathogen detection [6]. Second, in all cases, proper sample collection and transport to the laboratory must be carried out [7]. In the case of BCs, as reported in the 2015 review by Snyder [8], factors such as skin antisepsis, blood volume, number of BC specimens collected, the timing of BC collection, and delays in incubation time significantly influence the sensitivity, interpretation, and clinical relevance of BCs. The volume of blood to inoculate in the BC bottles and the time needed to incubate these bottles in intelligent incubation systems are important to note. The recommendations of the Infectious Diseases Society of America (IDSA)/American Society for Microbiology (ASM) state that the volume of blood to be cultured must be related to the weight of the patient. Thus, inoculated in a single aerobic vial, between 1 and 5 ml (1:5 dilution) are required in young children, while 10-20 ml (1:10 dilution) should be collected for culture in older children and adults and, divided into two vials (anaerobic and aerobic). The positivity rate increases between 3-5% for each ml of cultured blood. A delayed entry of blood culture bottles in the automatic incubation system negatively impacts the total detection time and decrease the recovery of some pathogens. Implementing automatic loading of BC bottles with a 24h/7d strategy shortens the time to diagnosis significantly and increases the BSI diagnostic rate. Finally, the diagnosis of sepsis is based on clinical symptoms and there are no specific diagnostic criteria or a single standard diagnostic test. When a BC is positive, it is usually too late to implement the measures that would be applied to allow an early diagnosis. The laboratory should be advised before all clinical suspicion of sepsis in order to accelerate and prioritize the processing of the patient's samples. This process should ideally be supported by computer systems that facilitate the generation of alerts and control of response time. At the Vall d'Hebron University Hospital [9], a preconfigured profile has been incorporated into the request for laboratory tests, both for adult and paediatric cases, and it is adapted to the determinations that must initially be carried out in these patients, which include peripheral BC (at least two sets), complete blood count, basic biochemistry, coagulation study, acid-base balance, and fundamentally biomarkers. The request for this profile triggers a notification system by messaging (e-mail and phone SMS) that alerts the hospital and laboratory sepsis code manager and the intensive care unit and microbiology on-call teams. The entry of samples requested under this profile generates a patient label that is visible on all the samples processed or to be processed, and is deactivated after 72 hours if the BC no longer remain positive. The positivity of BCs of with this label generates an alert on the screen for the duty team to control the samples that require urgent processing. In the case of urine, a visible sign to alert the laboratory technicians is created to prioritize the sample processing. Additionally, if the sediment is positive, a direct urine disk-diffusion antibiogram is performed.

Other actions to speed up obtainment of results from additional samples are currently being studied.

ANALYTICAL PROCESS

At present, new molecular diagnostic techniques, such as Xpert MRSA/SA BC test (Cepheid®), BD MAX StaphSR Assay (BD Diagnostics), Eazyplex MRSA (Amplex Diagnostics), PNA FISH™ rapid diagnostic tests (AdvanDx's), Bio-Fire® FilmArray® 2 panel BC identification (bioMérieux), Gram-negative and Gram-positive Verigene BC test (Luminex of Diasorin), ePlex BCID Panels (Roche Diagnostics), BC Unyvero cartridge (Curetis) and Sepsis Flow chip (Master Diagnostica of VITRO) [10] allow working from positive BCs. These tests detect the presence of the most frequent aetiological agents of bacteraemia/sepsis and, in many cases, some of the main resistance genes, in a time between 30 minutes and 5 hours. Technology applicable to direct blood is needed for real advances in time and to save the hours of pre-incubation of BC [10]. Some approaches are already available, such as the T2 magnetic resonance technique (T2MR from T2 Biosystems), which combines paramagnetic nanoparticle sensors that are detected by T2MR and allows the detection of the most relevant target bacterial and yeast species in direct blood with very high sensitivity (>95%) and at extremely low concentrations of only one cell/ml of blood. As a limitation, it is difficult to interpret some of the discrepancies found between the results of these techniques and those of traditional cultures, considering the clinical context. Thus, BC remains the gold standard for diagnosing bloodstream infection/sepsis [11].

BC media and incubators have been improved in order to detect exigent species, including anaerobic species, and reduce the time to BC positivity. When a BC is positive, it is still important to perform the Gram stain smears to determine the clinical value of the isolation and individualize the most adequate management according to the clinical context of the patient. Working with pellets undoubtedly saves significant time in both the performance of matrix-assisted laser desorption/ionization-time of flight mass spectrometry that allows microorganism identification in less than 1 hour from BC positivity, and in obtaining a direct antibiogram for which there

are already specific European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [12] as well as devices with different technological approaches. Some laboratories have worked with their traditional commercial systems (VITEK, MicroScan) directly from BCs for more than 20 years. Although this work method was not endorsed by any of the expert committees (EUCAST/CLSI) mainly due to the absence of standardization of the inoculum (suspension of the pellet obtained after centrifugation or supernatant drops), the excellent correlation with the antibiogram carried out from the colony and that provides results the same day of BC collection, has led to this practice continuing until now. The rapid AST (RAST) method by EUCAST and different commercial devices of accurate and fast (2-7h) susceptibility testing of positive BCs are currently available. These devices are based on automatically monitoring bacterial growth in the presence of different antibiotic concentrations using nephelometry (Alfred AST (Alifax), PNA FISH plus morphokinetic cellular analysis (Accelerate Pheno System, BD), microfluidics with live cell fluorescent microscopy for the study of cell responses in a linear antibiotic concentration gradient (QuickMIC of Gradientech), high-speed time-lapse microscopy imaging of bacteria in broth (ASTar of QLinea), inoculum standardization from liquid colony obtained by FAST System (Qvella), array detection of volatile emissions produced by microbial growth (VITEK® REVEAL™ of bioMérieux) and flow cytometry (FASTinov) [13].

The incorporation of one technique or another must be adequately assessed, with special attention given to determine the impact of the results obtained on the patient's prognosis, which is difficult to measure [14] and requires close collaboration with the clinical team.

POST-ANALYTICAL ACTIONS

The results obtained require adequate assessment of the clinical context of the patient. The implementation of electronic records in most hospitals provides timely knowledge of patient status and antibiotic coverage. The results of diagnostic tests, especially BCs, must be clearly and immediately reported to the clinical team, especially if the patient is not receiving adequate empirical antibiotic therapy. For this, it is essential that laboratories be open 24h/7d [15]. The clinical microbiologist should not be limited to simple issuing reports by conventional means; automatic alert systems should be developed through immediate messaging or by specific Web Apps that transmit critical information and obtain return confirmation of the display of these results and, if possible, information as to whether they have generated any action on the treatment. These improvements will help improve antimicrobial stewardship and optimize patient care. Likewise, clinical microbiologists must be integrated within the multidisciplinary team that manages these patients and, even in patients who are not haemodynamically stabilized, discuss the possible need for de-escalation of antibiotic treatment according to the spectrum of the results emitted. The human and economic efforts performed to reduce the time to issuing laboratory results are useless if they are not reflected in real and immediate action in the patient that contributes to better treatment and prognosis.

CONCLUSIONS

In order to reach a rapid and adequate sepsis microbiological diagnosis, it is essential to review all the procedures followed in the selection, collection, and processing of the different samples in order to create rapid workflows, individualized routes and automated alert systems, which allow improving diagnostic yield and avoiding unnecessary loss of time. Furthermore, in the case of positive results, reports must be available within 24 hours after the onset of sepsis. When incorporating new technologies into the diagnostic process, these must be assessed based on the expected impact on the patient and the possibility of actual incorporation, considering the technical requirements, the laboratory workflow, and the availability of staff and hours during which the laboratory is open. In centres in which a sepsis code is implemented, it is also essential that a Microbiology Service is available with a 24/7 model and a medical team capable of acting based on the results at any time of the day or night.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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Nosocomial pneumonia: Current etiology and impact on antimicrobial therapy

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ABSTRACT

Nosocomial pneumonia is an infection with high clinical impact and high morbimortality in which *Pseudomonas aeruginosa* plays a priority role, especially in the critically ill patient. Conventional antipseudomonal treatments, historically considered as standard, are currently facing important challenges due to the increase of antimicrobial resistance. In recent years, new antimicrobials have been developed with attractive sensitivity profiles and remarkable efficacy in clinical scenarios of nosocomial pneumonia including bacteremia, mechanical ventilation, infections with multidrug-resistant organisms or situations of therapeutic failure. This new evidence underscores the need to update current clinical guidelines for the antimicrobial treatment of nosocomial pneumonia, especially in the most critically ill patients.

Keywords: Hospital-acquired pneumonia, *Pseudomonas aeruginosa*, Enterobacterales, Ceftolozane-tazobactam, Ceftazidime-avibactam

INTRODUCTION

Hospital-acquired pneumonia, in addition to vascular catheter-associated infections, urinary tract infections, and surgical site infections, stands as one of the most common healthcare-associated infections and, in addition, represents a noteworthy cause of mortality.

Hospital-acquired pneumonia is the leading cause of healthcare-associated infection in intensive care units (ICU) [1] in Spain. More specifically, ventilator-associated pneumonia accounts for 41.06% of infections in ICU with an incidence rate of 13.83 per 100 mechanically ventilated patients [2]. The mortality rate of nosocomial pneumonia, regardless of mechanical ventilation, is in the range of 20-50%, and can reach up to 75% when there is structural or functional alteration of the respiratory tract or when the infection is caused by a multidrug-resistant microorganism [3,4].

To date and until the implementation of molecular techniques to optimize treatment, the choice of antimicrobial agent in hospital-acquired pneumonia in the early stages is usually empirical. This decision is usually based on the severity of the clinical picture, the results of previous cultures, knowledge of the local epidemiology and an assessment of the risk factors for multidrug-resistant microorganisms. Appropriate antimicrobial treatment therefore remains a challenge.

As recommended in the 2016 guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), empirical antimicrobial treatment for healthcare-associated pneumonia should comprise piperacillin-tazobactam, an anti-pseudomonal cephalosporin, levofloxacin, or an anti-pseudomonal carbapenem. Additionally, coverage against methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered if the patient has risk factors. In cases of respiratory distress, high mortality risk, or recent receipt of intravenous antibiotics within the prior 90 days, double anti-pseudomonal coverage is advisable [5].

When determining the antimicrobial treatment for patients with hospital-acquired pneumonia, it is crucial to consider the following factors: (i) Etiology and resistance patterns: understand the causative agent and its resistance profile; (ii) Pharmacokinetics and pharmacodynamics: with special attention to how the drug distributes and its concentration within the infection site to ensure its effectiveness and (iii) Clinical trials experience: consider insights gained from relevant clinical trials in making treatment decisions.

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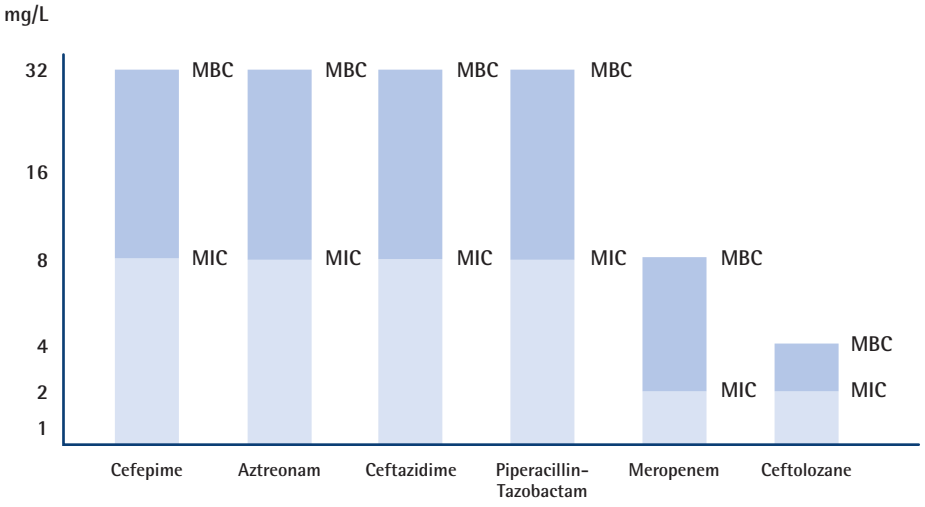

Figura 1 | **MIC-MBC difference, impact on clinical efficacy and selection window for resistant pathogens (intra-treatment resistance) [12].**

THE ETIOLOGY OF NOSOCOMIAL PNEUMONIA AND RESISTANCE PATTERNS

In contrast to other healthcare-associated infection models, where *Escherichia coli* is typically the most common pathogen, hospital-acquired pneumonia presents a different pattern. *P. aeruginosa* stands out as the most frequent etiological agent, accounting for up to 17.73% of isolates in cases of ventilator-associated pneumonia. Among enterobacteria, *Klebsiella pneumoniae* is the most prevalent, found in 8.72% of isolates (which is half as common as *P. aeruginosa*). *E. coli* is isolated in 6.59% of cases of ventilator-associated pneumonia [2].

In Spain, the most common mechanism of antimicrobial resistance in *P. aeruginosa* is the combination of *ampC* and alterations in permeability, which can be attributed to porin deficiency or increased expression of efflux pumps [6].

According to the prevalence study of healthcare-associated infections in Spain, roughly 20-40% of enterobacterial isolates exhibit resistance to third-generation cephalosporins, including ESBL or *ampC* resistance mechanisms. Additionally, 2-16% of isolates demonstrate resistance to carbapenems. These figures are notably higher in the case of non-fermenting microorganisms, with approximately 25-30% of *P. aeruginosa* isolates exhibiting resistance to carbapenems) [1].

When considering only isolates from respiratory tract samples, the resistance rates for meropenem and piperacillin-tazobactam, which are considered the standard therapies [5], are as follows: 34.26% and 38.94%, respectively, for *P. aeruginosa*, and 11.32% and 30.88% for *K. pneumoniae* [2]. These figures align with other studies, indicating resistance rates of 25-30% for the pathogens typically associated with healthcare-associated pneumonia to these antimicrobials, which are commonly recommended in clinical practice guidelines [7]. Finally, the count of *P. aeruginosa* strains posing significant treatment challenges - defined as those showing resistance to multiple classes of antimicrobials, such as piperacillin-tazobactam, carbapenems, antipseudomonal cephalosporins, aminoglycosides and quinolones - has been increasing, reaching 13.8% in 2022 [8].

MICROBIOLOGICAL AND PHARMACODYNAMIC ADVANTAGES OF NEW ANTIPSEUDOMONAL DRUGS

Fortunately, following the release of the aforementioned antimicrobial therapy recommendations [5], new antimicrobial drugs with improved microbiological profiles have been developed. These drugs have undergone favorable assessments by regulatory agencies and have received therapeutic approval for the treatment of healthcare-associated pneumonia. Most important advantages of these new antimicrobial drugs is their more favorable resistance profile. In our country, the susceptibility of *P. aeruginosa* isolates to ceftazidime-avibactam and ceftolozane-tazobactam is 94.2-94.6%, respectively [9]. In a more recent study, in vitro sensitivity of isolates from respiratory samples, including *P. aeruginosa*, *K. pneumoniae*, and *E. coli*, exceeded 87%. Susceptibility was slightly lower in isolates with elevated carbapenem minimum inhibitory concentrations (MIC) [10].

In addition to the benefit in the spectrum, the new antibiotics provide advantages in the management of nosocomial pneumonia. The first is the stability in the sensitivity they maintain against isolation. Specifically, ceftazidime-avibactam and ceftolozane-tazobactam maintain MICs of 8 and 2mg/L respectively in carbapenem-resistant *P. aeruginosa* strains when MICs of cefepime, ceftazidime or piperacillin-tazobactam are ≥

Table 1 New antimicrobial drugs studies in hospital-acquired pneumonia.

	REPROVE [23]	APEKS-NP [24]	ASPECT-NP [25]
Study drugs	Ceftazidime-Avibactam vs Meropenem	Cefiderocol vs Meropenem	Ceftolozane-Tazobactam vs Meropenem
Patients	726	292	726
APACHE II [(Mean (SD)]	14,5% (4.01) vs 14.9% (4.05)	16.0% (6.1) vs 16,4% (6.9)	17.5% (5.2) vs 17.4% (5.7)
Bacteremia	4,68 %	9,59% (32)	6,06%***
Mechanical ventilation at baseline	43,11 %	59,93%	100%
Clinical cure rate	68,8% vs 73,0% (difference -4.2 [95% CI -10.76 to 2.46])* 77·4% vs 78·1% (difference -0.7 [95% CI -7.86 to 6.39])**	65% vs 67% (difference -2.0 [95% CI - 12.5 to 8.5])*	54.4% vs 53.3% (difference 1.1 [95% CI -6.2 to 8.3])* 63.8% vs 64.7 (difference -1.3 [95% CI -10.2 to 7.7])**
Microbiological eradication	55.6% vs 64.1% (difference -8.6 [95% CI -18.65 to 1.64])	48% vs 48% (difference -1.4 [95% CI -13.5 to 10.7])	73.1% vs 68.0% (difference 4.5 [95% CI -3.4 to 12.5])
Mortality at day 28	8.1% vs 6.8% (difference 1.4 [95% CI -2.48 to 5.35])*	20.0% vs 22.0% (difference -1.2 [95% CI -12.1 to 10.0])* [32]	24.0% vs 25.3% (difference 1.1 [95% CI -5.1 to 7.4])*

*Clinically modified intention-to-treat population, ** Clinically evaluable population, *** Gram-negative respiratory pathogen only.

32 or 128 mg/L [11]. The second is the lower cross-resistance, compared to classical antipseudomonal antibiotics (piperacillin-tazobactam, ceftazidime, cefepime), which after having been previously used in the patient, more easily induce resistance to the antibiotic used or to any of the others. This generally occurs due to overexpression of ampC or of the Mex AB/XY expulsion pump [12]. However, this cross-resistance is exceptional among the new antipseudomonal antibiotics, which are stable against ampC de-repression and are not affected by either loss of porins or hyperactivity of efflux pumps [13].

Ceftazidime-avibactam also includes the important addition of coverage against *Enterobacteriaceae*, including strains carrying high resistance (ESBL, ampC, OXA-48, KPC). The main added advantage of ceftolozane-tazobactam lies in its proximity between MIC and MBC (Minimal bactericidal concentration). This particularity is useful to reduce or avoid the selection window that facilitates the emergence of resistant strains. For example, the difference between MIC and MBC in ceftazidime, aztreonam, cefepime or piperacillin-tazobactam ranges between 8 and 32mg/L, with high and maintained concentrations of the antibiotic being necessary to avoid the selection of resistant strains. In the case of meropenem the difference between MIC and MBC is 2 to 8mg/L, however, in ceftolozane-tazobactam it is 2 to 4mg/L [12] (Figure 1). First consequence of this proximity between MIC-MBC are the lower likelihood of intra-treatment antimicrobial resistance (recorded in the ceftolozane-treated group with respect to the meropenem-treated group in the ASPECT-NN study) [14). Second, it is ability to achieve a lung and plasma epithelial linning fluid (ELF) concentration that ensures a 86-95% probability of target attachment (PTA) at the approved and marketed dose of 3g/8h [15,16]. Therefore, this proximity between MIC and MBC favors microbiological eradication, especially in situations where achieving optimal drug concentrations at the site of infection is challenging, such as cases involving capillary leakage, alterations in the ventilation/perfusion (V/Q) ratio, respiratory distress and severe pneumonia.

The distribution and concentration of antimicrobial drugs within the infection site are crucial factors of paramount importance. The diffusion of ceftazidime-avibactam and cefiderocol to the ELF is approximately 30-35% of the plasma concentration [17,18]. This percentage can be increased reaching of up to 60% the plasma concentration by extending the infusion time, ensuring that drug concentrations remain above the MIC throughout the dosing interval [18]. On the other hand, meropenem-vaborbactam has slightly lower sensitivity figures [19]; however, it manages to reach concentrations in the ELF of up to 60% of the plasma concentration. This characteristic can be particularly valuable in the treatment of critically ill patients [20]. Diffusion of ceftolozane-tazobactam to the ELF, it is approximately 30-40% of the plasma concentration.

Even more effective treatment could be achieved with these new drugs, using the same dose, but extending the infusion time. Ceftazidime-avibactam is stable at room temperature (22-25°C) for up to 4 hours after reconstitution [21] and ceftolozane-tazobactam for up to 24 hours [22], and can be administered as a continuous infusion. In both drugs, the pharmacodynamic ratio of posological effectiveness (T>MIC 50%) is above 99%, extending the infusion to the limit of its molecular stability.

CLINICAL TRIALS EXPERIENCE

To the best of our knowledge, three studies have been

Table 2 **Antipseudomonal recommendation against multi-drug resistant *P. aeruginosa* in the main guidelines for the treatment of antimicrobial-resistant gram-negative infection**

Guideline	Antipseudomonal recommendation against multi-drug resistant *P. aeruginosa*
Mensa J. et al. Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: Guidelines by the Spanish Society of Chemotherapy. (2018) [12])	In order of preference: Ceftolozane-tazobactam > Ceftazidime-avibactam > Meropenem > Ceftazidime or Piperacillin-tazobactam ± Amikacin or Colistin
Paul M. et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli. (2022) [28])	Ceftolozane-tazobactam Insufficient evidence available for: Imipenem-relebactam, Cefiderocol or Ceftazidime-avibactam
Pintado V. et al. Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria. (2023) [29]	Ceftolozane-Tazobactam Alternatives: Ceftazidime-avibactam, Imipenem-relebactam, Colistin, Cefiderocol, Fosfomycin
Tamma PD et al. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. (2023) [30])	In order or preference: Ceftolozane-tazobactam > Ceftazidime-avibactam > Imipenem-relebactam Alternative: Cefiderocol

conducted to evaluate the outcomes of these new drugs in the treatment of hospital-acquired pneumonia. When comparing the use of ceftazidime-avibactam (REPROVE) [23], cefiderocol (APEKS-NP) [24], or ceftolozane-tazobactam (ASPECT-NP) [25] to meropenem, no significant differences were observed in terms of clinical cure, microbiological eradication, or 28-day mortality. This information is summarized in Table 1.

A more in-depth analysis of the patient characteristics in these studies reveals that the patients included in the ASPECT-NP study [25] are clinically more critical. They exhibit higher APACHE II scores, experience bacteremia more frequently, and importantly, all of them are under mechanical ventilation therapy. This heightened severity of patient conditions enhances the significance of the study's results.

Ceftolozane–tazobactam also demonstrated non-inferiority to meropenem in terms of clinical cure rates among patients who had previously received unsuccessful antibacterial therapy (such as piperacillin-tazobactam, anti-pseudomonal third-generation cephalosporins, or quinolones) for the current episode of hospital-acquired pneumonia before entering the study [24]). Interestingly, high clinical success rates were achieved in patients who received ceftolozane-tazobactam as secondary therapy (84.8%) or salvage therapy (86.2%), as well as in those with life-threatening *P. aeruginosa* infections (80.7%), including 31.7% with hospital-acquired pneumonia, over one-half of *P. aeruginosa* strains being extensively drug-resistant (XDR), and with 78.2% of isolates displaying resistance to at least one carbapenem [26]. Moreover, in a post-hoc analysis of ASPECT-NP, focused on ventilated patients with hospital-acquired bacterial pneumonia and confirmed microbiological isolation in a respiratory samples [27], the likelihood of death by day 28 was 2.3 times higher in participants treated with meropenem as opposed to ceftolozane-tazobactam (with a 95% confidence interval ranging from 1.2 to 4.5). This observation was made after accounting for other clinically relevant factors.

While it is accurate that the clinical practice guidelines for hospital-acquired pneumonia have not been revised since 2016, in recent years, several scientific societies have formulated antimicrobial treatment recommendations for addressing infections caused by resistant gram-negative bacteria, particularly for invasive infections involving *P. aeruginosa* [12,28-30]. These recommendations take into account the use of these new antimicrobial drugs, and valuable advice and treatment suggestions for hospital-acquired pneumonia can be derived from them. These recommendations are summarized in Table 2.

Therapeutic appropriateness significantly influences patient outcomes. The choice of medication has an impact on mortality rates, even when early diagnosis and intervention are in place. Data from 2021 year's ENVIN report underscores that appropriate antibiotic treatment for hospital-acquired pneumonia is currently at 76,34% [2], echoing the gap previously discussed concerning both microbiological and clinical aspects.

In cases where patients lack risk factors for multi-resistant microorganisms or signs of respiratory distress, following the 2016 guidelines [5] is a suitable approach during the initial stages. However, when patients present these risk factors, exhibit respiratory distress or have progressed beyond the seventh day of illness, it's advisable to consider a transition to

newer antibiotics such as ceftolozane-tazobactam or ceftazidime-avibactam [31]. These alternatives may offer a more effective and appropriate treatment in such specific cases.

In summary, hospital-acquired pneumonia is a prevalent and life-threatening medical condition, often caused by *P. aeruginosa* as the primary pathogen, along with less frequent occurrences of other enterobacteria. Conventional antimicrobial agents, historically considered as the standard treatment, now face significant resistance challenges. Fortunately, newer antimicrobial drugs with improved sensitivity profiles and additional advantages have emerged, proving highly effective even in the most critical clinical scenarios, including cases involving bacteremia, respiratory distress, mechanical ventilation, infections with multidrug-resistant organisms, and instances of therapeutic failure. These developments underscore the need for an update to the existing clinical practice guidelines for antimicrobial treatment of hospital-acquired pneumonia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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Risk of severe COVID in solid organ transplant recipients

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ABSTRACT

Despite the fact that COVID is today not a life-threat for the general population, recipients of solid organ transplantation should be viewed as a high risk group for severe COVID. Repetitive doses of SARS-CoV-2 vaccine still fail to protect SOT recipients from infection, disease or even death caused by COVID. A more frequent need for medical care may initially place these patients at greater chances of SARS-CoV-2 infection. Immunosuppression after engrafting and underlying medical conditions that led to the practice of SOT contribute to more risk of severe infection. Immunosuppression also blunts the intensity of humoral and cellular responses after vaccination, even when several booster doses have been administered. Still, vaccination is the best strategy to prevent a fatal outcome in case of SARS-CoV-2 infection, with a particular reduction in mortality. SOT recipients should be considered a high-risk population that need yearly SARS-CoV-2 vaccination.

Keywords: COVID-19, Solid Organ Transplant recipients, risk of infection, vaccination, prognosis

The pandemic caused by the severe-acute-respiratory-syndrome coronavirus type 2 (SARS-CoV-2) has complicated the practice of solid organ transplantation (SOT) in several ways: i) reduction in the availability of donors [1]; ii) reduced response to SARS-CoV-2 vaccination; iii) risk of severe coronavirus infectious disease (COVID) from immunosuppression, both in vaccinated and unvaccinated subjects.

Focusing on the clinical evolution of COVID in patients that had undergone SOT, a large metanalysis done before the wide availability of SARS-CoV-2 vaccine demonstrated that transplanted patients had more risk of severe COVID and more mortality as compared with not transplanted individuals [2]. A total of 1,485 SOT recipients, enrolled in 15 studies with retrospective design, were evaluated; most grafts involved kidneys, but other transplanted organs as liver, heart, lungs, pancreas were included in the analysis. Other medical conditions were commonly present in transplanted subjects, as hypertension, diabetes, and chronic lung, kidney, or liver disease. The number of non-transplanted patients that served as comparators exceeded 15,000 subjects, which also had the beforementioned comorbid conditions at lower frequencies. The mean age of participants was in general comparable in all studies. The risk of need for ICU admission was greater in transplanted as compared with non-transplanted individuals (OR: 1.57 [95% CI, 1.07-2.31], p=0.02), although need of mechanical ventilation was not different between these groups (OR: 1.19 [95% CI, 0.89-1.58], p=0.24). With respect to fatal outcomes, mortality resulted significantly greater among SOT recipients as compared with controls (OR: 1.40 [95% CI, 1.10-1.79], p=0.007); this difference remained significant when transplanted patients were compared with controls matched for age, sex and comorbidities (HR: 1.42 [95%CI, 1.01-2.00], p=0.046). It may be concluded that recipients of SOT are burdened with greater morbidity and mortality associated with SARS-CoV-2 infection. The reasons for this association may be firstly the greater number of comorbidities in transplanted patients--such as hypertension, diabetes, chronic kidney, liver lung or heart disease, and others—[3, 4], so that the need of SOT may be viewed as a surrogate marker of underlying medical conditions that worsen the prognosis of COVID.

The negative effect of immunosuppressive therapy over the evolution of COVID is a subject of debate. After SARS-CoV-2 infection, the enhancement of intense immune reactions, where the release of cytokines has a central role [5], play the main part in the pathogenesis of severe COVID. Therefore, SOT recipients may see some benefits from being under treatments that blunt the overstimulation of immune responses

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against SARS-CoV-2 infection, in particular inflammatory responses [6], of which the indication of corticosteroids for patients with severe respiratory distress is a paradigmatic example [7]. Some drugs in particular, as calcineurin inhibitors or mycophenolic acid, may reduce the risk of severe COVID in part from the anti-inflammatory effect, but also with potential antiviral properties [8-10]. The negative aspect is that also T-cells producing virus-specific cytokines have been shown to be inhibited under immunosuppressive drugs [11]. In general, taking the results of different studies that analyze humoral and cellular response against SARS-CoV-2, it may be concluded that the initial immune response to primary infection may be weaker in transplanted subjects under immunosuppressive therapy, what may make infection more aggressive, although inflammatory responses may be less intense; this makes difficult to predict the net effect of immunosuppression on the severity of COVID in SOT recipients. However, survivors to COVID are capable of generating a long-lasting immunity, in part related with the greater severity of the first infection [12-15].

Given this in general more risk of complicated COVID among SOT carriers, this population was primed for early SARS-CoV-2 vaccination. As could be expected, immunosuppression is translated into lower response rates to mRNA vaccines when comparing SOT recipients –including kidney, liver, lung, heart-- to healthy individuals [16, 17]. In particular, cellular immune responses are lower in SOT recipients even when compared, not just with healthy controls, but also with other causes of immunosuppression as primary immunodeficiencies or HIV infection, defect that mostly compromises the durability of the protective effect of the vaccine [18]. In a prospective study including 200 SOT recipients (live, kidney and lungs) and another 200 controls, the humoral and cellular responses to mRNA vaccine were lower in the former after 6 months of follow-up. Positive IgG titers against the SARS-CoV-2 spike were seen in only 36% of transplanted participants, but in 97% of controls; with respect to cellular immunity response was positive in 13% versus 60%, respectively [19]. Of particular concern, it seems that lung transplant is associated with lower humoral responses after vaccination (10-40%) when compared with kidney (40-60%) or liver (30-40%) transplant [20-25].

Despite the reduced protective effect of vaccination, the benefit in transplanted patients is very significant. In a large study including nearly forty thousand SOT recipients that had received two doses of SARS-CoV-2 vaccine, vaccination was not associated with a reduction in the risk of infection, but provided a 20% reduction in the risk of death in case of COVID as compared with unvaccinated patients [26]. Again, patients with lung transplantation and subjects older than 50 years, those that have weaker response to vaccination, were found with higher risk of death. Several studies have shown that immunosuppressive regimens that include glucocorticoids, mycophenolate mofetil, calcineurin inhibitors and belatacept are associated with less response to vaccination. Still, the benefit of vaccination among transplanted individuals is greatly reduced as compared with healthy subjects. Studies done in the general population showed more than 90% vaccine efficacy both in terms of lower rate of infections and lower mortality. It is important to emphasize that SOT recipients who received vaccine doses had a better chance of survival compared with unvaccinated SOT recipients in case of COVID.

The administration of booster doses after primary vaccination provides stronger immunity in SOT recipients, which includes humoral response, neutralizing activity, and cellular response [27]. Still, around 20% of patients with SOT may still remain seronegative after several doses of SARS-CoV-2 vaccine. However, it seems that the greater the number of vaccine doses the lower the chances for severe COVID [28]. Comparative studies suggest that mRNA vaccines have better performance that adenovirus vector vaccines in SOT carriers [29].

It may be concluded that patients with SOT are exposed to a greater risk of severe COVID, although immunosuppression is not the unique or even the major factor contributing to this worse outcome, as underlying medical conditions are also strongly associated negative factors. Although the response to vaccine is weaker in transplanted individuals, booster doses seem to improve protection but not yet to levels comparable to the general population. For all these reasons, in the current scenario of starting vaccination with the fifth or even the sixth dose of SARS-CoV-2 vaccine, SOT recipients should be considered first-line candidates for this yearly schedule that includes other high-risk populations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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Therapeutic strategy in the transplanted patient

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ABSTRACT

The SARS-CoV-2 infection prognosis has dramatically changed as a result of population vaccination and the surge of omicron. However, there are still specific populations at risk of progression to severe diseases that require hospitalization or even at risk of death. The kidney transplant population is one of them. Consequently, when compatible symptoms appear, an early diagnosis should be sought in order to start specific antiviral treatment as soon as possible to avoid clinical deterioration of the patient. Antivirals have shown, in transplant patients, a decrease in the rate of hospitalization and death, especially with their early administration.

KEYWORDS: kidney transplant, COVID-19, donation

INTRODUCTION

The prognosis of SARS-CoV-2 infection has dramatically changed as a result of population vaccination, the immunity acquired naturally due to the infections suffered and the circulation of the omicron variant, with a lower pathogenic power. However, there are still hundreds of deaths every week in Europe, despite a low circulation of the virus, and the mortality of hospitalized patients for COVID-19 has been described as 7%, doubling the mortality rate of the influenza virus infection [1].

There are several risk stratification scores, both clinical [2-4] and analytical [5], which make it possible to identify patients at risk of progression, to select those who can be discharged adequately, avoiding inappropriate admissions, and safe avoiding patient return visits [6] and improving the quality of care provided in the different COVID-19 patient´s phenotypes described [7,8]. An outpatient care model with a high-resolution consultation after emergency discharge is effective for patients with COVID-19 without respiratory failure with clinical or analytical markers of unfavourable evolution [9].

At this time, most of the population suffers a mild viral infection, but there are specific groups that present a risk of poor evolution and may require hospital admission or even death. The vulnerable population is well identified: 1) elderly patients; 2) patients with comorbidity, especially when several accumulate; and 3) immunocompromised patients [10]. Although, due to the volume of patients, most complications are observed in elderly patients [11,12], immunosuppressed patients, including kidney transplant recipients, represent a population at high risk of progression to severe disease.

RISK OF PROGRESSION IN THE TRANSPLANTED PATIENT

Transplant patients are especially vulnerable to presenting poor clinical results due to their state of immunosuppression. This risk is particularly high among those who received immunosuppress treatment, those with a history of a neurological condition, and those with chronic kidney disease [10].

Coll E et al. showed that the incidence of SARS-CoV-2 infection in Spanish solid organ transplant and hematopoietic stem cell transplant patients was twice that than the one of the general population, with a median interval from transplant of 59-month, and the patients at highest risk were those with a lung transplant [13]. The mortality of the patients in this study was high, standing out 46% in lung transplant recipients, 28% in kidney transplant recipients, and 22% in liver and heart transplant recipients. However, the population included in the study is prior to the availability of vaccines and effective antiviral treatments.

Finally, it is important to remember that the duration of the immune response in transplant patients after the third

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dose of the vaccine decreases significantly, so booster doses are required [14].

ANTIVIRAL TREATMENT EFFICACY

We currently have 2 antiviral treatments that have shown high efficacy in preventing the appearance of complications in SARS-CoV-2 patients infected when administered in the initial stages: nirmatrelvir/ritonavir and remdesivir. The latter has also shown its effectiveness in preventing mortality in severe patients who require hospital admission.

Considering patients with mild or moderate disease, administration of nirmatrelvir/ritonavir within the first 5 days of symptoms has shown a lower hospitalization rate among the general population who received it compared to those who did not, with a reduced risk of 51%. This beneficial effect has been observed even in those patients who had received ≥3 mRNA vaccines against COVID-19, observing a 50% risk reduction, and for all age groups depending on the comorbidity they presented [15]. Schwartz et al reported the results of an analysis of real-life data showing a 51% reduction in mortality in patients treated with nirmatrelvir/ritonavir [16].

Antiviral treatments have also shown efficacy in the solid organ transplant population with mild or moderate disease, with a reduction in the rate of hospitalization or death at 30-day follow-up from 30% to 10% in treated patients compared to those who did not receive specific treatment [17-19].

Limited data and guidelines exist for the use of nirmatrelvir/ritonavir in tacrolimus-stabilized solid organ transplant recipients for the treatment of mild to moderate coronavirus disease. This is due to concerns about the effect of using it concomitantly with calcineurin inhibitors, due to significant drug-drug interactions between ritonavir, a strong cytochrome P4503A inhibitor, and other cytochrome P4503A substrates, such as tacrolimus. Dewey KW et al reported their experience with patients discontinuing tacrolimus and starting nirmatrelvir/ritonavir 10 to 14 hours after the last dose of tacrolimus. Tacrolimus was discontinued and then restarted at a modified dose 48 hours after completion of nirmatrelvir/ritonavir therapy. No patient experienced tacrolimus toxicity or acute rejection within 30 days of cessation of nirmatrelvir/ritonavir treatment. The authors conclude that nirmatrelvir/ritonavir can be used safely with close monitoring of tacrolimus levels and appropriate dose adjustments [20].

The advantage of using remdesivir in this population profile, such as kidney transplant recipients, is the absence of significant drug interactions and the possibility of using it in patients with renal failure. There are several studies showing the efficacy of a 3-day course of remdesivir, administered within 7 days of symptom onset, in preventing severe disease in patients with COVID-19 who received a solid organ transplant. Receiving remdesivir significantly reduces the hospitalization rate in outpatients who received it and in preventing clinical worsening in transplant patients who were hospitalized for reasons other than COVID-19 [21]. A study that included kidney, lung, liver, and heart transplant recipients, who were mostly vaccinated against COVID with ≥3 doses, showed that early administration of remdesivir significantly decreased the hospitalization rate, with the number of patients needed to treat to prevent a hospitalization of 15, and no patients who received early remdesivir requiring ICU admission or died. Therefore, it could be concluded that the early administration of 3 doses of remdesivir independently reduced the severity of the disease [22]. Finally, it should be noted that the studies recently carried out with remdesivir have led to the authorizing of its administration in patients with renal failure, given that the studies carried out have shown its safety in participants with severely reduced renal function [23].

Regarding patients with severe disease requiring hospitalization, studies have shown the benefit of remdesivir administration to prevent disease progression and the need for mechanical ventilation, as well as reducing mortality [24]. The sooner antiviral treatment is started, the greater the protective effect we can expect, but we must not forget that immunosuppressed patients can present viral replication even weeks after the onset of symptoms. A recent retrospective routine clinical practice study of hospitalized immunocompromised adults with COVID-19 in the US showed that initiation of remdesivir within the first two days of hospital admission was associated with significant reductions in mortality at 14 and 28 days, regardless of the circulating variant and the clinical situation of the patient [25].

DONATION FROM PATIENTS WITH COVID-19

The decision to transplant organs from donors with SARS-CoV-2 infection must be considered seeking a balance between the risk of disease transmission to the recipient and the scarcity of available organs. However, it seems safe in the short term in terms of death and graft loss [26]. A preliminary Spanish experience supports the safety of the use of organs other than the lungs from SARS-CoV-2 PCR positive donors, in line with other previous series, establishing that if the cause of death was not COVID-19, the donation could be considered [27]. A recent systematic review showed that the use of organs, except the lung, from donors with SARS-CoV-2 infection appears to be a safe practice, with a low risk of transmission, regardless of the presence of symptoms at the time of collection. Low viral replication (Ct > 30) was safe among non-lung donors, even if they had persistent symptoms at the time of collection [28].

CONCLUSION

Kidney transplant patients are at increased risk of SARS-CoV-2 infection and poor clinical outcome. Early diagnosis of this infection should be sought in order to start specific antiviral treatment as soon as possible. In patients with mild or moderate disease, antiviral treatment administered in the initial phases of the disease has been shown to protect them from progression, avoiding hospitalization and death. In pa-

tients with severe disease, administration of remdesivir decreases the risk that patients will die or require mechanical ventilation. The presence of SARS-CoV-2 infection does not necessarily prevent the deceased from being a candidate for donation, so they should be considered as a potential donor.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SARS-CoV-2 infection in solid organ transplant recipients: Experience with molnupiravir

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ABSTRACT

Solid organ transplant recipients (SOTR) constitute one of the groups at highest risk for the development of severe COVID-19. However, evidence on the effectiveness of treatments for SARS-CoV-2 infection in this group of patients is scarce. Molnupiravir is an orally administered antiviral drug that has demonstrated effectiveness in reducing the risk of progression to severe COVID-19 in high-risk outpatients, mainly in the unvaccinated population. Although its effectiveness is lower than that of other antivirals, on many occasions it is the only therapeutic option in transplant recipients given the absence of pharmacological interactions with immunosuppressive treatment, the oral route of administration and the good safety profile.

Keywords: molnupiravir, transplantation, COVID-19

INTRODUCTION

Coronavirus disease (COVID-19), caused by SARS-CoV-2, continues to be a significant cause of morbidity and mortality worldwide. With the emergence of less virulent viral variants and widespread vaccination, the incidence of severe forms of SARS-CoV-2 infection is concentrated in certain high-risk populations, such as immunosuppressed patients, including solid organ transplant recipients (SOTR). In the last two years, different therapeutic options for SARS-CoV-2 infection have been developed, targeting both severe forms of the disease and preventing progression in mild forms in high-risk patients. The therapeutic arsenal includes corticosteroids and immunomodulators, monoclonal antibodies and antiviral drugs such as remdesivir, nirmatrelvir/ritonavir, and molnupiravir.

Molnupiravir is a drug with antiviral activity whose mechanism of action consists in the induction of an accumulation of mutations in the viral genome by means of its incorporation into the RNA chain through RNA polymerase. It is administered as a prodrug, requiring two enzymatic steps to transform into the active form (beta-D-N4-hydroxycytidine-triphosphate) [1]. It is administered orally, and the recommended dosage is 800 mg every 12 hours for 5 days. It is a drug with a good safety profile, showing an adverse event rate similar to placebo in the MOVe-OUT pivotal clinical trial [2].

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MOLNUPIRAVIR VERSUS OTHER TREATMENTS

Molnupiravir versus monoclonal antibodies. The main advantage of molnupiravir over monoclonal antibodies is that it retains its antiviral activity against the different circulating variants of SARS-CoV-2. However, most of the monoclonal antibodies on the market lose neutralizing capacity against the new variants that are currently the most common (mainly Omicron BQ 1.1) [3].

Molnupiravir versus other antiviral drugs. Unlike the orally administered antiviral nirmatrelvir/ritonavir, molnupiravir has no relevant drug interactions and does not require adjustment for renal or hepatic function. This is especially relevant in SOTR, in whom the administration of ritonavir increases the levels of other drugs metabolized through cytochrome P450, such as calcineurin inhibitors or mTOR inhibitors.

The main advantage over remdesivir is the oral route of administration, which facilitates outpatient treatment in patients with mild SARS-CoV-2 infection. On the other hand, remdesivir is not recommended in patients with glomerular filtration rate < 30 ml/min or elevated liver enzymes.

However, molnupiravir has some disadvantages compared to other antiviral drugs. Although no comparative clinical trials have been performed between them, in pivotal clinical trials evaluating effectiveness versus placebo in non-hospitalized, unvaccinated patients with mild SARS-CoV-2 infection, mol-

nupiravir showed a relative risk reduction of hospitalization or death at day 28 of 30% [2] versus 89% for nirmatrelvir/ritonavir [4] and 87% for remdesivir [5].

On the other hand, molnupiravir is contraindicated during pregnancy and lactation as it has been associated with a teratogenic effect in animal models.

THERAPEUTIC POSITIONING

The different international organizations and national health agencies position molnupiravir as a therapeutic option in patients with non-severe SARS-CoV-2 infection at high risk of progression to severe disease, generally as an alternative to other antiviral drugs considered preferential.

In this regard, the *WHO living guidance for clinical management of COVID-19* in its latest update of January 2023 establishes a weak recommendation in favor of the use of molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children), similar to the recommendation established for remdesivir but behind nirmatrelvir/ritonavir [6]. As arguments for this recommendation, it points to the absence of long-term data on the safety of molnupiravir in relation to genotoxicity and the possibility of the emergence of resistance.

Similarly, the *COVID-19 Treatment Guidelines* of the US National Institutes of Health, updated in April 2023, places molnupiravir as a therapeutic alternative in nonhospitalized adults with mild to moderate COVID-19 who do not require supplemental oxygen at high risk of progression versus nirmatrelvir/ritonavir and remdesivir, which are considered preferential [7].

In the latest version of the document "*Criteria for evaluating the administration of new antiviral therapeutic alternatives against SARS-CoV-2 infection*", the Spanish Agency for Medicines and Health Products also places molnupiravir as an alternative therapeutic option in cases in which the administration of nirmatrelvir/ritonavir and remdesivir is contraindicated or not possible [8].

Finally, with regard to its availability, it should be noted that molnupiravir is not currently authorized for marketing in the European Union, although it has been recommended for use by the Human Medicines Committee of the European Medicines Agency.

CLINICAL EXPERIENCE

Experience in general population. Several clinical trials have evaluated the clinical and virological effectiveness of molnupiravir, with discordant results depending on the target population analyzed.

The MOVe-OUT trial evaluated the efficacy of molnupiravir in non-hospitalized, unvaccinated mild to moderate COVID-19 adults with a risk factor for progression to severe disease [2]. Molnupiravir demonstrated a reduction in the risk of hospitalization or death from any cause at day 29 (6.8% vs. 9.7%; difference 3% [-5.9% to -0.1%]).

Subsequently, the Phase III PANORAMIC clinical trial evaluated the efficacy of molnupiravir in patients with mild COVID-19 older than 50 years or with any risk factor for progression to severe disease [9]. More than 90% of patients had received at least three doses of the vaccine. In this study, molnupiravir was not superior to the standard of care in the combined endpoint of hospitalization or death within 28 days of randomisation. However, patients who received molnupiravir had an earlier symptomatic recovery. The representation of immunosuppressed patients in the PANORAMIC clinical trial was low (8.5%), and in particular the group of transplanted patients represented 1% of the total population. With regard to virological efficacy, in the AGILE CST-2 clinical trial molnupiravir did not show a greater clearance of viral replication in nasopharyngeal swabs compared to placebo [10].

In some real-life studies conducted during the period when Omicron was the predominant variant, molnupiravir has shown good results. In a retrospective study in hospitalized patients, treatment with molnupiravir was associated with lower 28-day mortality and need for corticosteroid and immunomodulatory therapy, with maximum benefit in patients older than 80 years who received molnupiravir within 5 days of symptom onset [11]. However, in this study, information on the vaccination status of the patients included was not available. In the same way, in another Propensity Score-matched cohort study conducted in non-hospitalized patients with any risk factor for progression to severe disease, treatment with molnupiravir was associated with a lower risk of severe COVID-19 or death at 28 days in the subgroups of non-vaccinated patients and in patients older than 75 years of age [12].

Experience in immunosuppressed patients including solid organ transplant recipients. There are few data on the use of molnupiravir in immunosuppressed patients, as they were often excluded from studies or their proportion of the total population was low.

In a post-hoc analysis of the MOVe-OUT clinical trial in the subgroup of immunosuppressed patients, molnupiravir was associated with a lower risk of hospitalization or death and increased clearance of infectious virus [13]. However, the results were not significant due to the small sample size (n=55). In most cases the immunosuppression status was active oncologic disease or well-controlled HIV infection; transplant patients accounted for less than 10% of the total.

Experience with molnupiravir in SOTR is scarce. In a retrospective study of 122 SOTR (renal, liver, and cardiac) with mild COVID-19, treatment with molnupiravir was associated with a 44% relative risk reduction of hospitalization or death [14]. In contrast to these findings, another retrospective multicenter study analyzed outcomes of 218 lung transplant patients with mild COVID-19, and only age and glomerular filtration rate < 30 ml/min were independent risk factors were associated with an increased risk of severe disease [15]. None of the treatments administered (molnupiravir, sotrovimab or remdesivir) had an

impact on outcomes. Different case series, with mainly kidney transplant recipients, without comparator, showed that molnupiravir resulted in improvement of clinical symptoms with no serious side effects [16-18]. Finally, in another case series of kidney transplant recipients, the results with molnupiravir were similar to remdesivir in the rate of progression to severe disease [19]. Neither treatment was associated with adverse effects or interaction with immunosuppressive therapy.

CONCLUSIONS

Molnupiravir is an antiviral with a good safety profile, which has been shown to reduce the rate of hospitalization and death due to COVID-19 in some selected populations, although with a lower efficacy compared to other available treatments.

Its main advantages over other therapeutic options in SOTR are its oral administration, its low rate of adverse effects and the absence of drug interactions with immunosuppressive treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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Clinical experience in the treatment of COVID-19 with monoclonal antibodies in solid organ transplant recipients

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ABSTRACT

Solid organ transplant (SOT) recipients are at high risk for complications from coronavirus disease 2019 (COVID-19). SOT recipients mount lower immunological responses to vaccines than general population and are at high risk for breakthrough COVID-19 infections. Passive immunotherapy in the form of anti-Spike monoclonal antibodies (MoAbs) may be an alternative for the prophylaxis and treatment of COVID-19 in these patients. SARS-CoV-2 has evolved by accumulating resistance mutations that have escaped the neutralizing action of most MoAbs. However, MoAbs directed at more conserved epitopes and that maintain effector functions could maintain efficacy in the treatment of these patients. According to published data, SOT recipients with low anti-spike antibody responses to vaccination could benefit from the use of MoAbs in pre-exposure prophylaxis, in the treatment of COVID-19 mild to moderate and severe COVID-19 with less than 15 days of symptom duration and low oxygen requirements. Combination therapy could be more effective than monotherapy for the treatment of mild-to-moderate SARS-CoV-2 infection.

Keywords: COVID-19, SARS-CoV2, Solid Organ Transplant recipients, Monoclonal Antibody.

BACKGROUND

Solid organ transplant (SOT) recipients are at high risk for complications from coronavirus disease 2019 (COVID-19) [1]. Several studies performed early in the pandemic suggest high rates of hospitalization, intensive care unit (ICU) admission, and mortality. Lung transplant recipients appear to have the greatest severity [2]. Over the time, the prognosis of these patients has improved, mainly due to prevention measures, the development of new antivirals and vaccination. Although after each new dose of vaccine, the proportion of recipients with antibody and celular responses rises, SOT recipients mount lower immunological responses to vaccines than general population and are at high risk for breakthrough COVID-19 infections [3-5]. In this setting, passive immunotherapy in the form of anti-Spike monoclonal antibodies (MoAbs) may be an alternative for the prophylaxis and treatment of COVID-19 in these patients.

EVOLUTION OF VARIANTS AND SUSCEPTIBILITY TO MoAbs

MoAbs are specific immunoglobulins produced in the laboratory by purifying the circulating B lymphocytes from convalescents from a SARS-CoV-2 infection and cloning the antibodies from the cells with specificity against the epitope selected as a therapeutic target. Subsequently, the MoAbs obtained undergo a selection process to identify those with the greatest affinity and neutralizing capacity.

From previous experience with other coronaviruses that cause severe acute respiratory syndrome (MERS and SARS), the Spike protein(S) was selected as the main target of these MoAbs, and in this way block cellular infection. Most of the neutralizing response after infection is concentrated within this Spike protein, specifically in the receptor binding domain (RBD), and within this receptor in the region that physically contacts the cellular receptor ACE2, called Receptor Binding Motif (RBM). The SARS-CoV-2 virus is constantly evolving, evading the host's immune response. In the different circulating variants of the virus, resistance mutations have mainly been selected in the RBM regions, which has led to a decrease in the neutralizing capacity of the different MoAbs with specificity against that binding site.

Among the MoAbs that have been available in our setting, casirivimab/imdevimab, tixagevimab/cilgavimab, or regdanvimab with specificity against RBM regions have lost their

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neutralizing capacity against the new variants. Sotrovimab is a MoAbs developed from serum from a SARS-CoV-1 infected survivor that shares a highly conserved epitope also on the Spike protein of SARS-CoV-2. This MoAbs blocked the ACE2 binding site outside of RBM which accumulated fewer escape mutations so it maintains effectiveness, although decreased, against the new omicron subvariants. Therefore, it is necessary to consult the sensitivity of the MoAbs to the predominant circulating variants at all times in order to indicate their use.

Although the main function sought in these mAbs is the ability to neutralize infection, there is increasing information indicating that the effector functions of antibodies could play an important role in protection against the most severe forms of COVID-19. This protection would be related to the functions of cytotoxicity, phagocytosis and stimulation of the cellular response mediated by antibodies. All of these effector responses reside fundamentally in the interaction of the crystallizable fragment (Fc) of immunoglobulins with the entire family of anti-Fc receptors present in different populations of immune cells [6]. Sotrovimab contains a 2 amino acid Fc-modification that is designed to improve bioavailability in the respiratory mucosa and preserve effector functions. Recent studies in vitro and in mice showed that sotrovimab binds avidly to all Omicron variants, promotes Fc dependent effector functions and protects mice challenged with BQ.1.1, the variant displaying the greatest loss of neutralization. Therefore, MoAbs with conserved Fc-dependent effector functions may contribute to protection against disease caused by emerging variants through elicitation of effector functions [7].

PRE-EXPOSURE PROPHYLAXIS

Some MoAbs have demonstrated effectiveness in pre-exposure prophylaxis in high-risk populations, although these clinical trials include a very small number of immunocompromised patients and SOT recipients are not represented [8,9]. A multicenter retrospective cohort study evaluated the efficacy of tixagevimab/cilgavimab in vaccinated SOT recipients in a real-world setting during the Omicron period. The study compared 222 solid organ transplant recipients (SOTRs) who received tixagevimab/cilgavimab for pre-exposure prophylaxis and 222 vaccine-matched solid organ transplant recipients who did not receive tixagevimab/cilgavimab. More than 50% of the patients in both groups had kidney transplants, but lung, liver and heart recipients, and multi-organ transplant recipients were also included. Breakthrough SARS-CoV-2 infections occurred in 11 (5%) of SOT who received tixagevimab/cilgavimab and in 32 (14%) of SOT in the control group ($p<.001$). Stratified analysis by organ type showed a significantly lower incidence of SARS-CoV-2 infection in kidney and lung transplant recipients who received tixagevimab/cilgavimab compared to those who did not, the number of patients included with transplants of other organs was very small, so no statistically significant differences were found. The efficacy of a dose of 150-150 mg of tixagevimab/cilgavimab was also compared to 300-300 mg and it was observed that the incidence rate of breakthrough SARS-CoV-2 infection was higher in those who received the lower dose. No significant differences were found in the incidence of breakthrough infection between the tixagevimab/cilgavimab and control groups in the subgroup of SOTRs who had prior SARS-CoV-2 infection [10]. An observational study in kidney transplant recipients at a single center showed no significant difference in the risk of symptomatic breakthrough Omicron infection between those who received tixagevimab/cilgavimab compared to those who had high-titer anti-spike antibody responses to vaccination but did not receive tixagevimab/cilgavimab [11]. According to these results, the recipients who would benefit most from the use of MoAbs in pre-exposure prophylaxis are those with low anti-spike antibody responses to vaccination.

MILD TO MODERATE COVID-19

MoAbs have reduced hospitalisation or death in outpatients with mild to moderate COVID-19 in high-risk patients, including immunocompromised patients [12,13].

We do not have randomized clinical trials in patients with SOT, but several observational studies and case series have been published. Dhand et al reported their experience regarding the use of sotrovimab in 51 SOT recipients (most of them during the Omicron-predominant period) with at least 21 d of follow-up. These include 28 kidney, 11 liver, 9 heart, 2 liver/kidney, and 1 heart/kidney recipients. Only one patient experienced progression of COVID-19 symptoms requiring 5-d hospitalization and steroid therapy. Five patients required hospitalization unrelated to COVID-19 diagnosis. None of the patients required intensive care or died [14].

In another report of 88 patients who received one intravenous dose of 500 mg of sotrovimab (35 kidney, 18 lung, 17 heart, 15 liver, and 3 dual-organ recipients), ten percent (9/88) required hospitalization for COVID-19 after sotrovimab, including 1 admitted on the same day as infusion and 1 for a cerebrovascular accident 2 w after infusion. Of these 9 patients hospitalized after sotrovimab, 8 did not require supplemental oxygen and 1 required 2 L/min of oxygen via nasal cannula. No episodes of graft rejection or graft loss were observed, and no patients in this cohort required mechanical ventilation or died [15].

Probably the largest series corresponds to the retrospective cohort study by Yetmar et al, which included 361 SOT recipients, 92 (25.5%) receiving bebtelovimab and 269 (74.5%) receiving sotrovimab. The most common transplanted organ was the kidney (42.4%), 21,9% liver, 17,2% heart, 5,8% lung and 44 (12.2%) had received multiple transplanted organs. 3,3% of patients who received bebtelovimab and 3% of patients who received sotrovimab required hospitalization for COVID-19, including three (0.8%) who were admitted to the ICU (all of them received sotrovimab). Four patients died within 30 days of COVID-19 diagnosis; one was unvaccinated, one was fully vaccinated without a booster dose, and two were fully vaccinated with a booster. Two had received bebtelovimab and

the other two had received sotrovimab. The causes of death were an acute respiratory failure from progressiveCOVID-19, subarachnoid hemorrhage, and two were from unknown causes. The patient who died from progressive COVID-19 was fully vaccinated, boosted, and received bebtelovimab [16].

The main limitation of these studies is that they are observational studies without a control group. Kamar et al compared the outcome of SOT patients who were given monoclonal antibodies to an historical control group. Sixteen SOT patients (12 kidney, 1 simultaneous kidney-pancreas, 1 combined kidney-liver, and 2 heart-transplant patients) that presented after February 25, 2021 were treated with monoclonal antibodies, while the 32 remaining patients that presented before this date were considered as a control group. After a follow-up of 39 (10–74) d after the injection of monoclonal antibodies, none of these 16 patients developed a severe respiratory illness defined by the need for high oxygen support, while 15 of the 32 control patients developed a severe respiratory illness (46.9%, P = 0.007), requiring high flow nasal oxygen (n = 7) or orotracheal intubation (n = 8). Three patients from the control group deceased during follow-up [17].

Although we only have observational and retrospective studies, most of them without a control group, from the results obtained we can conclude that the use of MoAbs in SOT recipients with mild to moderate COVID-19 reduces the rate of progression and death.

SEVERE COVID-19

The use of MoAbs in hospitalized COVID-19 patients is controversial. While RECOVERY adaptative trial showed that MoAbs could reduce 28-day mortality in patients admitted to hospital with COVID-19 who were seronegative (and therefore not able to mount a humoral immune response), TICO platform trial found that MoAb LY-CoV555 did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure [18,19].

Few studies have evaluated the efficacy of treating hospitalized patients with severe COVID-19 (requiring oxygen therapy) with MoAbs in immunosuppressed patients. A spanish multicenter retrospective cohort study included 32 patients, 15 out of them were SOT recipients (9 lung, 4 kidney, 2 heart and 1 liver) aimed to describe the safety and efficacy of sotrovimab in severe COVID-19 immunocompromised hosts between October 2021 and December 2021, in a setting with predominance of mutant-rich variants. Most of them were fully-vaccinated but anti-spike antibodies were undetectable. At sotrovimab infusion, all patients had bilateral interstitial pneumonia with low flow nasal cannula oxygen supplementation. Only one transplant patient had respiratory progression and none died. in the cohort as a whole it is observed that PaFi greater than 210 at infusion was associated with a lower rate of respiratory progression (11.5% (3/26) versus 66.7% (4/6), p=0.005) and those receiving sotrovimab within the first 14 days from symptom onset had a lower progression also (12.0% (n=3/25) vs 57.1% (n=4/7), p=0.029) [20]. Therefore, immunocompromised patients (including SOT recipients) hospitalized for severe COVID-19 with less than 15 days of symptom duration and low oxygen requirements may benefit from MoAb treatment.

COMBINATION THERAPY

Cellular immunity is a key contributor to acute disease control and determinant for the severity of the disease. However, a loss of humoral immunity, even with preserved cellular immunity, is a significant contributor to the risk of impaired SARS-CoV-2 clearance [21]. As we have previously indicated, SOT recipients frequently show a low rate of anti-Spike (anti-S) immunoglobulin G (IgG) seroconversion after full vaccination. This insufficient humoral response leads to a prolonged viral replication, which ultimately causes a more extended and severe COVID-19. In this setting, the use of passive immunization treatments, such as MoAb, in combination with direct-acting antivirals could overcome the humoral deficit and prolonged viral replication in these patients.

Our experience, which is pending publication and which we partially reported in the 2023 ECCMID, includes 304 immunocompromised patients with mild-moderate SARS-CoV2 infection, of which 114 were SOT recipients (69 lung, 20 liver, 16 heart and 12 kidney), 21 received combination therapy with sotrovimab 500 mg single dose plus either a 3-day course of remdesivir or a 5-day course of nirmatrelvir/ritonavir and 93 received monotherapy with remdesivir, nirmatrelvir/ritonavir or sotrovimab. Most of them were fully vaccinated (90,1%) with a median time since last dose of 5 months (3-7 months). During follow-up (90 days) 4 SOT patients (3 lungs and 1 liver) presented COVID-19 progression to severe COVID-19 and 1 lung transplant recipient died, all of them had received monotherapy. All patients who progressed to severe COVID-19 had anti-S IgG titers less than 750 BAU/mL. Therefore, in SOT recipients with low vaccination response combination therapy including sotrovimab plus an antiviral agent may be more effective than monotherapy for the treatment of mild-to-moderate SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Mpox global outbreak: update in epidemiology, clinical spectrum and considerations in prevention and treatment

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ABSTRACT

Mpox is the most prevalent Orthopoxvirus infection in humans. Several clinical characteristics of mpox distinguish this disease from other rash illnesses. Complications are not uncommon. New therapeutics and vaccines are likely to change the course of the disease, especially in immunocompromised individuals. Clinicians must ensure that access to treatment and prevention measures are guaranteed especially in this particular population. This review exposes the epidemiology, clinical spectrum and updated considerations in treatment and prevention within the mpox global outbreak.

Keywords: Mpox, Monkeypox, Orthopoxvirus.

BACKGROUND

Mpox (formerly known as monkeypox) is a zoonotic viral disease caused by epitheliotropic viruses of *Orthopoxvirus*, from the family *Orthopoxviridae*. Since 2001, approximately 20 years after the cessation of universal vaccination against smallpox, the incidence of the disease has increased, becoming the most prevalent *Orthopoxvirus* infection in humans [1]. The disease in humans remained endemic in Central and West African countries, though sporadic outbreaks were reported out of these areas.

EPIDEMIOLOGY

Varied potential factors have contributed to mpox reemergence, such as waning vaccine-derived immunity, improved surveillance, ecologic shifts and human interactions with wildlife [2]. There are two distinct genetic clades of the mpox virus: the Central African clade (Congo Basin, clade I), and the West African clade (clade II). Clade II encompasses two subclasses: IIa and IIb. Clade IIb is responsible for the global outbreak of 2022. The disease caused by clade I is considered to be more severe and more easily transmitted. Cameroon is the only country where both clades of the virus have been found [3], and it is considered the geographic division of the virus. On May 2022, multiple EU Member States reported suspected or confirmed cases of mpox, with no epidemiological links to endemic areas. This is the first time that chains of person-to-person transmission of mpox have been reported throughout the world. Mpox spread rapidly and the World Health Organization (WHO) declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC) on July 2022 until May 2023. In total, 111 countries worldwide have reported more than 87,500 cases, with 141 deaths. The 10 most affected countries globally are United States of America (n= 30,194), Brazil (n= 10,941), Spain (n= 7,551), France (n= 4,146), Colombia (n= 4,090), Mexico (n= 4,017), Peru (n= 3,800), The United Kingdom (n= 3,742), Germany (n= 3,691), and Canada (n= 1,484). Together, these countries account for 84.2% of the cases reported globally. Overall, 96.4% of cases with the available data are men, with a median age of 34 years (IQR 29-41) [4]. The ongoing outbreak is largely developing in men who have sex with men (MSM) networks; in Europe, 97% of cases have been documented in MSM. Generally, severity has been low, with few reported hospitalizations and deaths [4]. Viral transmission from person to person may occur by direct contact with the skin lesions of an infected host, with their body fluids, respiratory secretions, and contaminated fomites. Transmission by respiratory particles requires close and prolonged contact. Vertical transmission has also been described. A few infections have resulted from injury with sharp instruments, skin piercing and tattooing. Due to its routes of transmission sexual relations facilitate contagion, and it is close contact during sex the dominant form of transmission in the current outbreak. Some individuals can spread mpox virus to others 1-4 days before symptoms appear [3].

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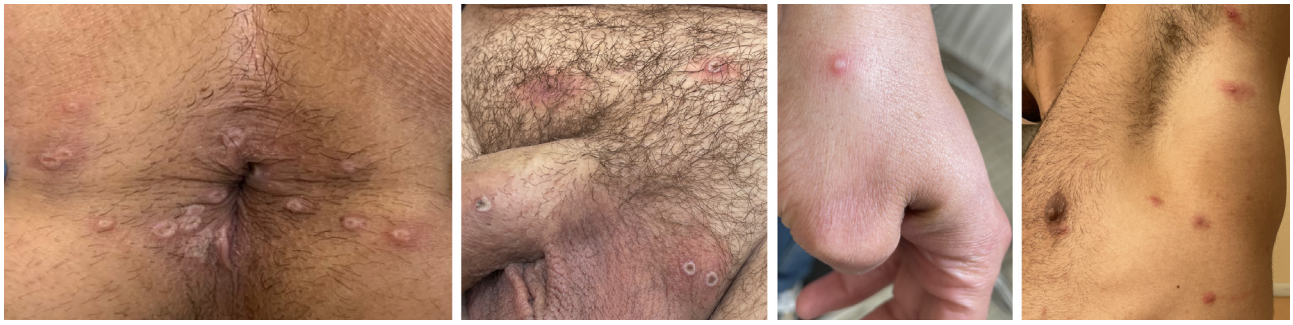

Figure 1 | **Patients with Mpox treated in Sandoval Center showing characteristic lesions.**

CLINICAL SPECTRUM

The clinical course of mpox has three stages. The first stage is the incubation period, which usually lasts 5-15 days. It is followed by an invasion period (between days 1-5), as the virus spreads through blood and the lymphatic system to internal organs and subsequently to the skin. It presents as fever, headache, lymphadenopathy, myalgia, and intense fatigue. Enlarged lymph nodes are firm, tender and sometimes painful, and are a distinct feature of mpox. The final stage and hallmark feature of mpox is a disseminated vesiculopustular skin rash, which begins 1-3 days after the effervescence of fever, but some studies show that this rash can appear before the onset of the fever [5]. The most affected areas are perioral, genital, and perianal regions, but also trunk, extremities and it can include palms and soles. The rash undergoes several phases, presenting first as enanthem, macules, papules, vesicles, pustules and finally crusts, over the course of 7-21 days (Figure 1).

Upon 2-4 weeks, successive outbreaks of skin lesions may appear, with lesions in different stages. The number of lesions vary from a few to several hundreds in immunocompromised patients. Complete removal of scabs can take up to 4 weeks since the onset of symptoms. Pitted scars and areas of hypo or hyperpigmentation may remain once all the scabs have fallen off. Anatomically, anogenital lesions are reflective of sexual practices [5]. Clinical distinction between rash illnesses is difficult. Given the similarities between smallpox, mpox and varicella, some clinical characteristics must be taken into account. The presence of large lymphadenopathy is distinctive of mpox. Varicella rarely has a prolonged febrile period, which is usually mild, and the rash progresses more quickly and rarely affects palms and soles. Additional rash illnesses that should be included in the differential diagnosis are secondary syphilis, measles, coxsackie, drug-associated eruptions, scabies, yaws, other herpetic infections and more rarely rickettsialpox [6]. Given the difficulty in clinical distinction between rash illnesses, diagnostic assays are an important component to the identification of *Orthopoxviruses*. The optimal samples for mpox diagnosis come from skin lesions: the fluid of vesicles and pustules, sometimes with the need of removing dry crusts to take a good sample (avoiding sharps instruments). If there are no skin lesions pharyngeal and rectal swabs might be a good option for the diagnosis. Polymerase chain reaction (PCR) is the laboratory test of choice due to its high accuracy (93.2-96.3%), sensitivity (90-100%), specificity (88.2-100%), positive predictive value (94.9-100%) and negative predictive value (87.9-100%) [7].

COMPLICATIONS

High prevalence of HIV and other sexually transmitted infections (STIs) have been reported in the mpox outbreak. People living with HIV have been particularly affected, representing approximately 40% of total mpox patients [8]. Disseminated and necrotizing forms of mpox have been described in individuals with HIV with inadequate immunovirological control, driving some authors to suggest that mpox could be included as an AIDS-defining condition [9]. Severe cases occur more frequently in children, pregnancy and in the immunocompromised. Complications (Figure 2) include pain management, secondary bacterial infections (including abscesses requiring surgical drainage), paraphimosis, phimosis due to scarring, pneumonia and respiratory distress, sepsis, encephalitis, multiple scars, keratitis with vision loss, abortion and myocarditis [10]. Severe outcomes and sequelae are more frequent among non-vaccinated patients. The case fatality rate in the current outbreak is <1%. Though uncommon, reinfections have been reported [11].

TREATMENT

Mpox is usually self-limited, with symptoms lasting 14-21 days. Supportive and symptomatic treatment should be performed. In complications due to secondary bacterial infections, antibiotics with activity against normal skin flora should be used. Several antivirals have been approved for the treatment of mpox. Tecovirimat is an oral or parenteral antiviral with *in vitro* activity against *Orthopoxviruses*. It inhibits the p37 protein involved in the formation and release of encapsulated virions. It may shorten the duration of illness and viral shedding.

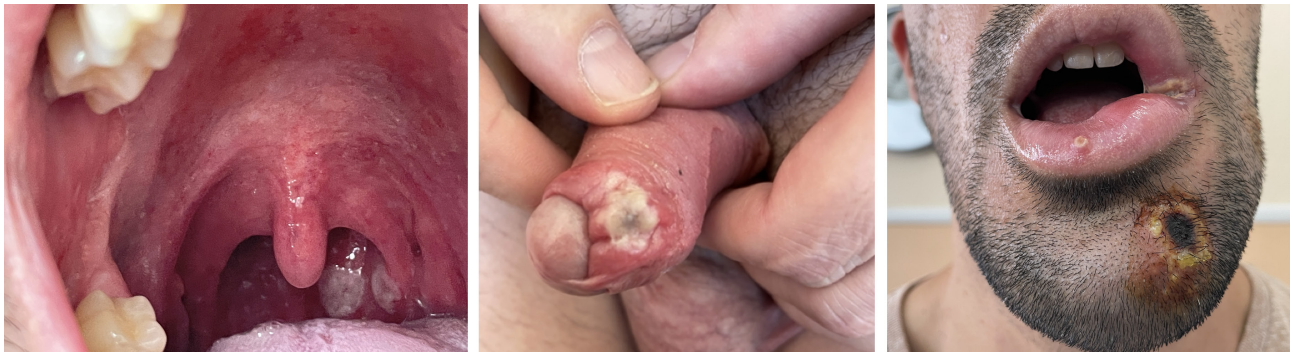

Figure 2 | **Pharyngeal lesions that avoid intake, genital ulcers with poor analgesic management and secondary skin bacterial infection as complications of mpox.**

It is the antiviral of choice. Tecovirimat is only approved for patients with severe illness (myocarditis, encephalitis, keratitis…) and/or patients with affected anatomical regions that can cause serious sequelae, and patients at high risk of severe disease according to clinicians' judgement [12]. All antivirals and even vaccinia immune globulin may be always considered under clinical trials.

PREVENTION

Small case series have reported mpox virus DNA detection in bodily fluids (semen) after healing of skin lesions, raising concern on the risk of onward transmission. Due to this consideration, WHO recommends patients to abstain from sexual intercourse until all skin lesions have crusted, the scabs have fallen off and a fresh layer of skin has formed underneath. The use of condom should be advised for 12 weeks after recovery to prevent potential transmission of mpox, though recent findings suggest that this period could be reduced [13]. Other preventive measures include: avoiding direct contact with skin lesions and respiratory secretions of infected patients, avoiding contact with objects, fabrics and surfaces that have been used by mpox patients, use of personal protective equipment (PPE) for health personnel, and isolation of patients until all skin scabs have fallen off.

VACCINATION

There is a vaccine available in Europe that is called Imvanex, commercialize in USA with the brand name Jynneos. It is an attenuated-live virus vaccine approved for the prevention of smallpox and mpox. It is administered intradermally as two doses of 0.1 ml separated 28 days in people aged 18 and over, and 0.5 ml doses subcutaneously in children, pregnant women and the immunocompromised. It is contraindicated in people allergic to chicken proteins, ciprofloxacin, gentamicin or benzonase. Indications in Spain as pre-exposure prophylaxis include people who maintain risk sexual practices (especially MSM) and people with occupational risk such as health professionals with no access to personal protective equipment (PPE). Regarding post-exposure prophylaxis, the vaccine is approved for close contacts of confirmed cases especially those with high risk of severe disease (immunosuppressed, pregnancy, children) and for health and laboratory personnel who have had close contact without PPE or incidences handling samples of patients with confirmed or suspected mpox cases [14]. Recently, a study has been published about the coverage of Jynneos vaccine in USA. The estimated adjusted vaccine effectiveness was 35.8% for partial vaccination (one dose) and up to 66% for patients that received two doses (full vaccination) [15].

CONCLUSIONS

Mpox has become a global concern. It is important to distinguish it from other rash illnesses and to maintain high suspicion. Infection may be associated with complications, especially STIs, superinfection and pain management. Other complications are more prevalent in immunosuppressed individuals. Clinicians must recommend preventive measures and vaccination. Investigation into new potential treatments is compulsory, along with the understanding of the long-term effects and the virus itself.

CONFLICT OF INTEREST

Authors declare no conflict of interest. All pictures were obtained with verbal and written consent from the patients treated.

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Group A *Streptococcus* invasive infection in children: Epidemiologic changes and implications

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ABSTRACT

Group A *Streptococcus* (GAS) can cause a broad array of clinical manifestations and complications. Recently, in post COVID-19 postpandemic months, there has been an increased incidence and severity of invasive infections in the pediatric age group in Spain and other European countries with high morbidity, affecting mostly to young children, associated with seasonal peaks in incidence of viral respiratory pathogens. The increased in incidence and severity has not been associated with predominant GAS strains, but rather to the lack of immunity to both GAS and common viral respiratory infections due to isolation measures to prevent COVID-19. Due to the nonspecific initial clinical manifestations a high index of suspicion is necessary in order to initiate a prompt medical and surgical treatment when necessary to improve the outcome. Prevention strategies are needed as well as continuous microbiological surveillance of iGAS strains.

Keywords: Group A *Streptococcus* infection, infection, invasive, children

INTRODUCTION

Streptococcus pyogenes, also known as group A Streptococcus (GAS), an exclusive human pathogen, can cause a broad range of clinical manifestations and complications, from asymptomatic infections and minor illnesses, such as pharyngitis and impetigo (noninvasive disease), to very severe and deadly infections (invasive diseases) or postinfectious sequelae such as rheumatic heart diseases or poststreptococcal glomerulonephritis [1-3]. Invasive infection (iGAS), defined as laboratory isolation of GAS from any normally sterile site, or isolation of GAS from a non-sterile site in a patient with necrotising fasciitis or streptococcal toxic shock syndrome (STTS) occurs unfrequently, but may lead to sepsis, STSS, complicated pneumonia, meningitis, osteoarticular infections, deep abscesses, or necrotizing fasciitis with potentially fatal outcome [3], requiring a high index of suspicion to start early treatment. During the last decade, increased rates of iGAS disease in children have been reported in many countries [4-6].

EPIDEMIOLOGY

Children may have a higher risk of severe disease. The observed increased rates of infection along with the higher morbidity in the pediatric age group has led to an increase in iGAS notifications in children, particularly in those below 10 years of age [4-7]. Even though during the pandemic years of COVID-19, respiratory infections, including GAS, dramatically decreased due to lockdown, social distancing and the use of masks [8], a recent upsurge has been observed in Europe [5-7]. Early December 2022, the United Kingdom Health Security Agency (UKHSA) published a surveillance report on an unusual incidence of GAS tonsilitis, scarlet fever and simultaneously of iGAS infections with high morbidity and mortality and issued a warning to parents and clinicians about the high iGAS incidence among children [7,9]. Other countries in Europe, including Spain [6], are also reporting similar concerns of increased incidence and severity of GAS infections [6,7,9].

The respiratory tract and skin are the two main portals of entry for iGAS [4]. There are well-known risk factors associated with iGAS. Disease onset and progression can be very rapid, with high fatality rates, especially in young children and elderly, patients with comorbidities (diabetes or cardiovascular disease), immunocompromised, alcohol abuse, intravenous drug users, pregnant women and previous varicella infection [1,10]. Environmental factors such as number of household inhabitants and residential overcrowding have also been associated with iGAS [1]. Concomitant respiratory viral infection might also play a role on the incidence and severity of iGAS, particularly in children. Notably, during the 1918 influenza pandemic, streptococcal superinfections were important causes of death, which besides *Streptococcus pneumoniae* also included GAS [10]. GAS carrier has not consist-

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ently been associated with transmission, although occasional outbreaks with more virulent strains have been reported in children, also in Spain [11,12]. The ability of GAS to transmit quickly and efficiently throughout a closed population during outbreaks may potentially cause an upraise in invasive infection and may indicate a need for intervention to control GAS transmission.

The increased in incidence and severity has not been associated with predominant strains. In the largest study on the microbiology and epidemiology of iGAS disease in Spain, Villalón et al showed that the most prevalent emm types were emm1, emmm89, emm3 and emm4 [13]. In children, the most common emm in Spain type has been emm1 [13,14] in keeping with other European countries [14]. Although it is possible that changes in GAS genome could have led to increased transmissibility or virulence, there has been diversity of strains, and only a minority of cases are attributed to outbreaks [4]. By contrast, the recent upsurge in IGAS in children has been linked to marked seasonal peaks in incidence of respiratory viral pathogens (mostly RSV and influenza), after withdrawing the strict preventive measures against COVID-19 [7]. In addition, the lack of specific immunity to GAS and common viral respiratory tract infections during this isolation period may have predispose young children to higher rates and more severe infections after exposure. Recent studies show that up to 60% of iGAS in children UK had a concomitant viral respiratory tract infection [15].

ETIOPATHOGENESIS

The process of human infection by GAS is complex and multifactorial, involving both host and bacterial factors that contribute to its pathogenesis. Although the surface C-polysaccharide antigens are used to classify *Streptococcus* spp. into Lancefield groups, they have not a major involvement in virulence. By contrast, several virulence factors have been identified in GAS. The major virulence GAS appears to be the surface M protein which is encoded by the *emm* gene with marked immunogenic and virulence properties, including its role in phagocytosis inhibition and adhesion, and promoting a proinflammatory response that may lead to tissue destruction and dissemination. GAS is classified based on the sequence of the 5′ end of the gene encoding the M protein (*emm*). More than 230 *emm* genotypes have so far been identified. As protective antibodies can be generated against the M protein, it represents one of the most characterized vaccine candidates to date.

Other virulence factors of GAS include the hyaluronic capsule, streptolysin O, streptolysin S, streptococcal pyrogenic exotoxins A and B, and NAD glycohydrolase NADase. Bacterial exotoxins act as superantingens to trigger polyclonal T-lymphocyte activation by binding to class II major histocompatibility complex molecules, leading to an excessive release of proinflammatory cytokines and subsequent shock [1,10].

CLINICAL MANIFESTATIONS OF IGAS

iGAS occur predominantly in young children. In a large retrospective study conducted in a referral center in Madrid, the median age at diagnosis was 48 months [15]. Similarly, in a Spanish multicenter retrospective study of SGA bacteremias, most infections occurred in children below 4 years of age, with a median of 24 months [16]. The clinical manifestations of iGAS are varied and include cellulitis and subcutaneous abscesses, ENT abscess, pneumonia, osteoarticular infection, mastoiditis, necrotizing fasciitis, bacteremia and STTS [16]. Initial symptoms include an influenza-like illness prodrome, characterized by fever, chills, confusion, myalgia, nausea, vomiting and diarrhea. It is important to recognize cutaneous lesions that may be the portal of entry, including varicella lesions in settings where varicella vaccine has not been administered [2]. In addition, a suspicious sign at onset may be scarlatiniform rash. More unusual manifestations include meningitis, neonatal infections, peritonitis, gastrointestinal and endovascular infections [2].

Interestingly, in the clustered cases reported by the Spanish multicenter network for analyzing iGAS in Spain (PedGAS-net) in late 2022, there was a shift towards a lower age and presentation with pneumonia and pleural effusion as well as a significant increase in ICU admissions of iGAS compared to prepandemic years [6,17]. The overall mortality in this study was 1.8% [6]. Based on published series, the mortality reported ranged from 0-8% [2], still lower than that observed in adults [4]. Table 1 shows the main characteristics of the Spanish children included in PedGAS-net [6]

Table 1 Main characteristics of cases of iGAS reported in PedGAS-net [6]

	N=220
Demographics	
Gender (female)	95 (43.2%)
Age (months)	41.2 (19.3-81.0)
Syndrome	
Toxic shock syndrome	25 (11.4%)
Pneumonia	66 (30.0%)
Skin and soft tissue infections	so (22.7%)
Bone and joint infection	27 (12.3%)
Primary bloodstream infection	23 (10.5%)
Deep neck infections	22 (10.0%)
Mastoiditis	22 (10.0%)
Complications	1
	0 (4.5%)
Necrotizing fasciitis	21 (9.5%)
Abscess	42 (19.1%)
Pleural effusion	3 (1.4%)
Pneumothorax	14 (6.4%)
Acute kidney failure	
Disseminated intravascular coagulation	9 (4.1%)
Outcomes	
Intensive care admission	89 (40.5%)
Died	4 (1.8%)

IMPLICATIONS FOR TREATMENT AND PREVENTION

Due to the non-specific signs and symptoms of the initial clinical manifestations and the rapid course of iGAS in children a high index of suspicion is mandatory to start early treatment, including prompt and aggressive surgical debridement when necrotizing fasciitis is present [2,10]. Antibiotic therapy remains the mainstone for the treatment of both non-invasive and iGAS infection [10]. GAS remains universally sensitive to β-lactam antibiotics. If penicillin-allergic patients, the use of macrolides should be avoided for empiric therapy for iGAS, since resistance to macrolide frequently result in recurrent infection, treatment failure and poor patient outcomes, and vancomycin is preferred. Linezolid and daptomycin are active *in vitro*, but clinical experience in treating invasive GAS infections is limited [10]. The addition of and antitoxin antibiotic such as clindamycin or linezolid is recommended, particularly if necrotizing fasciitis, STTS, or clinical signs of toxin production by SGA (rash, gastrointestinal signs, hemodinamic instability) [1]. The optimal duration of adjunctive clindamycin is uncertain as data are limited, but at least a minimum duration of 3 to 5 days is recommended [10].

Although resistance to macrolides has been variable in Spain even with local differences in the same city, and frequent in some locations, the overall prevalence is decreasing, but still significant. In the large Spanish surveillance study of almost 2000 iGAS isolates analyzed over a 13-year period, the prevalence of erythromycin resistance was 8.9%, whereas clindamycin resistance remains low, around 4% [13]. As clindamycin resistance is increasing in some settings, clinicians need to order susceptibility testing when using clindamycin for adjunctive treatment. The effect of clindamycin resistance in invasive GAS infections remains unclear. A murine model found that inhibitory concentrations of clindamycin reduced both the size of skin lesions and activity of virulence factors, even in clindamycin-resistant GAS strains [10]. Nevertheless, in these cases linezolid is an option and has become more widely used in clinical practice as an adjunctive agent instead of clindamycin [2,10].

In addition, the use of intravenous polyvalent immunoglobulin must be considered in severe cases of iGAS in order to neutralize exotoxins involved and as immunomodulator of the proinflammatory stage [2].

Prevention of secondary cases is of utmost importance. A major step forward would be to maintain high coverage of varicella vaccine and include universal influenza vaccination in children. The inclusion of influenza vaccine in children in some regions in Spain is a major advance in struggling against the challenge of iGAS in children. The ability of GAS to transmit quickly and efficiently throughout a closed population together with the higher risk of vulnerable patients, including children, as well as such as mother-neonate pairs, highlight the importance of immediate notification and assessment of contacts and targeted prophylaxis should be considered [10]. In addition, continuous microbiological surveillance of iGAS strains should be monitored to determine the characteristics and evolution of circulating clones.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Clinical approach

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Current approach to skin and soft tissue infections. Thinking about continuity of care

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ABSTRACT

Skin and soft tissue infections are a common reason for patients seeking inpatient and outpatient medical care. Surgery is an essential part of managing in many episodes. Careful evaluation of antibiotic therapy could help clinicians in early identification to patients with treatment failure and to consider an alternative approach or a new surgical revision in "focus control". With the arrival of new drugs, there is a need to refine the appropriate drug's decision-making. Drugs with a long half-life (long-acting lipoglycopeptides such as dalbavancin or oritavancin), which allows weekly administration (or even greater), can reduce hospital admission and length of stay with fewer healthcare resources through outpatient management (home hospitalization or day hospitals). New anionic fluoroquinolones (e.g. delafloxacin), highly active in an acidic medium and with the possibility of switch from the intravenous to the oral route, will also make it possible to achieve these new healthcare goals and promote continuity of care. Therefore, management should rely on a collaborative multidisciplinary group with experience in this infectious syndrome.

KEYWORDS: Skin and soft tissue infections, cellulitis, source control of infection, antimicrobial therapy, new and long-acting antibiotics.

INTRODUCTION: CLINICAL AND EPIDEMIOLOGICAL IMPACT

Skin and soft tissue infections (SSTI) are a common reason for patients seeking inpatient and outpatient medical care with more than 14 million outpatient visits a year [1], and almost 900.000 inpatient admissions in the United States [2]. Between 2005 and 2010, approximately 4.8 SSTIs requiring medical attention occurred per 100 person-years annually among those aged 64 years and younger [3]. Although this number has remained relatively stable, the high incidence of SSTI, if properly treated, has enormous potential to reduce disease morbidity and health care utilization. Cellulitis is one of the most common forms of clinical presentation of SSTIs affecting the dermis and subcutaneous tissue. There has been a rise in cellulitis incidence and associated costs over the past few decades [1,4]. From 1998 to 2013, cellulitis hospitalizations doubled (approximately 650.000 cases), and costs increased by nearly 120% to more than $3.7 billion annually in the USA [5]. Cellulitis contributed 0.04% of the total global disease burden in 2013 [6]. In 2019, the global incidence and rate of disability-adjusted life years for cellulitis were 54.84 million and 6.96 per 1.000 person-years, respectively.

SSTI accounts, by some estimates, for 3-30% of all hospital visits to the emergency departments (ED) [7,8] and is one of the five entities with the greatest variability in clinical decisions [9]. An estimated 12-40% [10,11] of SSTI seen in the ED are later admitted to the hospital, and 0.7% to intensive care unit [12]. Sepsis occurs in 4-8% of all patients who suffer from complicated skin and soft tissue infections (cSSTI), in which signs or symptoms related to sepsis may occur [13]. Severe SSTIs with sepsis are relatively frequent, and they are responsible for about 10% of all cases of septic shock [14]. Following pneumonia (55–60%) and abdominal infections (25%), cSSTI are the third most frequent cause of severe sepsis or septic shock [15]. Necrotizing soft tissue infections (NSTI) are almost always complicated by severe sepsis or septic shock [16].

SSTI comprehend a wide spectrum of conditions ranging from superficial skin abscesses that may be safely managed as an outpatient basis to dramatic presentations with extensive necrosis of underlying structures and sepsis-related organ failures resulting in major functional sequelae or death, such as necrotizing fasciitis (one of the main kinds of NSTI) [17]. Early initiation of adequate antimicrobial therapy is the essential

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Table 1 Main features and details associated with increased likelihood of NSTI

Clinical characteristics	Laboratory parameters
Rapid progression of cellulitis or fasciitis	Progressive hyperlactatemia
Cellulitis refractory to antimicrobial treatment	Renal failure (decreased creatinine clearance or glomerular filtrate abnormalities)
Pain out proportion to examination	Hyponatremia (serum sodium < 135 mmol/l)
Tenderness beyond area of erythema	Leukocytosis (white blood cell count > 15.000 cell/µl) or leukopenia (< 3.000 cell/µl)
Cutaneous anesthesia	Haemostasis disorders, prolonged clotting times
Bullae, hemorrhagic blisters	Elevated C-reactive protein together with probably very high procalcitonin values
Dusky appearance of skin	Rhabdomyolysis (creatine phosphokinase elevations and/or lactodehydrogenase)
Crepitus	Hyperglycemia or hypoglycemia (underlying diabetes mellitus decompensation)
Systemic toxicity	
Fever that does not respond to treatment, or unexplained hypothermia	

NSTI: necrotizing soft tissue infections (e.g. necrotizing fasciitis, myonecrosis, gas gangrene).

key to improve outcomes in patients with life-threatening SSTI, along with prompt surgical evaluation, source control with repeated debridement and removal of necrotic tissues when required, and resuscitation procedures, such as fluid administration, vasopressors infusion, intravenous immunoglobulin therapy in case of associated staphylococcal or streptococcal toxic shock syndrome (STSS), and other sepsis directed cares [18]. Severe SSTI –in particular necrotizing fasciitis and STSS– is often associated with aging and comorbidities, such as diabetes mellitus, chronic renal failure, arterial occlusive disease, intravenous drug abuse, morbid obesity, liver diseases and immunosuppression.

DEFINITIONS AND SPECTRUM OF PROGNOSTIC SEVERITY

SSTI, cSSTI, and NTSIs refer to the terminology and concept of the set of infections in this location that are seen by clinicians in the real world. Acute bacterial skin and skin structure infections (ABSSSI) are a common and heterogeneous group of diseases that ranges from superficial uncomplicated entities to life-threatening disease. According to the terminology introduced by the Food and Drug administration, ABSSSI include cellulitis, erysipelas, mayor skin abscess and wound infections [19]. The objective of this definition is to provide a regulation that makes it possible to homogenize the episodes of SSTIs and to compare the different antibiotic treatments (old and new), using agreed and pre-established parameters, and to make it easier for regulatory agencies to evaluate randomized clinical trials rigorously and accurately, in order to be able to position each new antimicrobial drug [20].

The cause of the SSTI is confirmed in about half of the patients, with current evidence suggesting the predominant role of *Staphylococcus aureus* including methicillin-resistant strains (MRSA) [21], *Streptococcus pyogenes* and other β-haemolytic streptococci; however, in some regions Gram-negative bacteria are increasingly reported as a cause of monomicrobial or polymicrobial infections, being involved up to 30% of the cases in some studies [22,23].

Severity of illness due to SSTI loosely correlates with depth of skin structure involvement, though there is no universally agreed upon severity scoring system. Severe SSTI include necrotizing fasciitis, STSS and myonecrosis/gas gangrene. In addition, patients having any SSTI meeting criteria for severe sepsis or septic shock or having a quick Sequential Organ Failure Assessment (SOFA) score at least 2 will be considered to have a severe SSTI [24]. NSTIs are frequently complicated by sepsis or septic shock and are the main example of severe SSTIs [25]. Several factors can make SSTI complicated or severe. Some of these factors are patient specific (e.g., immunosuppression), others have to do with local wound conditions (e.g., rapid progression) or treatment patterns (e.g., necessity for significant surgical intervention) [26]. NSTI are serious, life-threatening infections of the soft tissues. When tissue death appears, the infection is referred to as necrotizing. An NSTI is an infection that can start in one location and spread to large areas of the body within just a few hours [25]. NSTI can affect any part of the body, but most commonly occur on the arms and legs and, rarely, on the neck or face. One of the classic signs of NSTI is pain out of proportion to the examination, referring to the fact that the infected area might look normal and may not be too tender but the patient has severe pain (Table 1). The area directly over the affected tissues can look red or grayish or swollen or can have blisters; however, because the actual infection is located deeper in the soft tissues, the top part of the skin may look normal. Sometimes, bacteria can produce gas, which can lead to a crunchy sensation when the affected skin area is pressed. Unlike a focal infection of the skin, an NSTI is a systemic disease, which means that it may cause fever, changes in heart rate and blood pressure, and changes in level of alertness (Figure 1) [24,25]. Diagnosis is made based on the

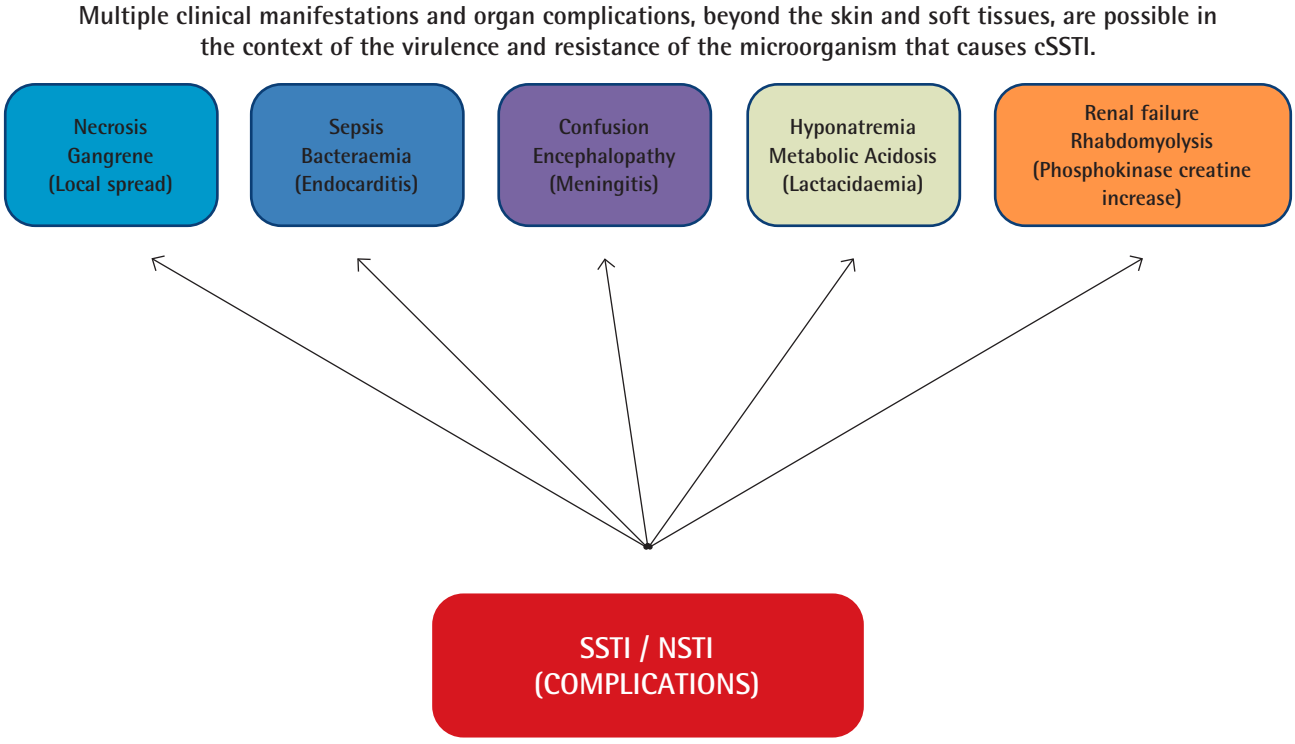

Figure 1 | **Complicated cellulitis and necrotizing fasciitis as local disease models with potential impact and serious systemic manifestations of sepsis and hematogenous dissemination**

SSTI: skin and soft tissue infections; cSSTI: complicated skin and soft tissue infections; NSTI: necrotizing soft tissue infections (e.g. necrotizing fasciitis, myonecrosis, gas gangrene).

patient's medical history, the physical examination, and the results of blood tests. If the diagnosis is not clear, an x-ray or computed tomography (CT) scan might help clarify the diagnosis. However, imaging is not recommended because it rarely establishes the diagnosis of an NSTI, and these tests delay the start of treatment [25,26].

In a recent prospective and observational study of 606 adult patients with cellulitis admitted to several Spanish hospitals, the factors associated with sepsis were: increased blood leukocytes and serum creatinine, blood culture drawn, modification of the initial antimicrobial regimen, and maximum length of cellulitis [27]. Regarding therapy, patients with sepsis associated to SSTI were related with poor treatment responses and more likely to undergo changes in the initial antimicrobial regimen, received more antimicrobials, received longer intravenous treatment, and underwent surgery more commonly than patients without sepsis with statistical significance [27,28].

For severe SSTI, intensive care, source control by means of early radical surgical debridement, and empirical broad-spectrum antimicrobials are required for the initial phase of illness and remain the cornerstones of therapy in NSTI. Owing to the rareness of NSTI, general clinical awareness is low and prompt diagnosis is often delayed. New diagnostic instruments (scoring systems, MRI) have either a low accuracy or are time consuming and cannot guide clinicians reliable currently. The choice of empirical agents depends on the type and location of SSTIs, place of onset (i.e. community acquired versus hospital-acquired), immune status, exposure history (animals, water, trauma), initial severity and whether the patient presents or not with specific risk factors (e.g. travel history) for multidrug-resistant bacteria (MDRB), with local epidemiology and prior antimicrobial use being among the main features to consider [29]. The value of adjunctive measures (intravenous immunoglobulin, hyperbaric oxygen therapy) is uncertain as well. Morbidity and mortality in NSTI remain high, ranging from 20 up to over 30% [26]. Further clinical research is necessary to shorten diagnostic pathways and to optimize surgical, antimicrobial, and adjunctive treatment.

NOVEL ASPECTS IN COMPREHENSIVE MANAGEMENT

In the modern comprehensive management of SSTI, sev-

Table 2 **Risk factors associated with methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTI)**

Risk Factors Associated with MRSA SSTI (including CA-MRSA)
Ethnicity (African Americans, Hispanic compared with Caucasian); recent travel (in Africa, Latin America or South East Asia)
Socioeconomic lower quintile, poor hygienic conditions, overcrowded housing, incarceration
Previous antibiotic therapy; recent (last three previous months)
History of MRSA: Previous colonization or *S. aureus* infection
Exposure: hospitalization in the previous 12 months, ICU admission, residence of long-term care facility, household contacts
Previous minor or major surgery
Intensive procedures and other instrumental techniques (e.g. image or radiological studies, central vascular catheters, implantable device)
Contact activities, such as daycare young children, contact sports activities, military service, contact with farm animals, insect bite injuries
Presence of underlying comorbidities: diabetes mellitus, peripheral vascular disease, cardiovascular disease, chronic wounds on extremities (often open), chronic renal disease, dialysis dependence, intravenous drug use,
Preexisting skin lesions (burns, eczematous dermatitis, etc.)
Purulent cellulitis
Hereditary (primary or congenital immunodeficiencies) or iatrogenic neutrophil disorder; immunosuppression

Methicillin-resistant *Staphylococcus aureus*: MRSA; skin and soft tissue infections: SSTI; Intensive care unit: UCI; Community-acquired methicillin-resistant *Staphylococcus aureus*: CA-MRSA.

eral guidelines for action must complement each other, mainly highlighting three: the so-called "focus control", the pharmacokinetic and pharmacodynamic optimization of antimicrobials and adjuvant measures.

The impact of surgical source control for severely ill patients with sepsis is underrepresented in clinical trials and the literature. Source control in cSSTI ranges from removal of central venous catheters or other device to radical debridement of extensive body areas. NSTIs serve as a model disease for the value of surgical measures in severe cSSTI [30]. Early diagnosis and timing of surgical intervention, the necessary extent of surgery and the assessment of adjunctive therapies (hyperbaric oxygenation, intravenous immunoglobulins) have been recently investigated [31]. The evidence for simple source control measures (i.e., wide opening and drainage of an abscess, limited debridement of infected tissue) remains low, but appears to be self-evident. Radical debridement of necrotic tissue (or even limb amputation) remains the standard of care for those patients with soft tissue sepsis because of NSTI. Specificities of NSTI with tissue necrosis and local ischemia resulting in hindered tissular diffusion are consistent with the need for urgent and aggressive surgical debridement of necrotic tissues. Surgical treatment should be performed within the first 12 h after admission. NSTI are a medical emergency. The key to treatment is emergency surgery to remove as much of the affected tissues as possible. This debridement may be extensive and disfiguring. Although a combination of antibiotics is used to help the body fight the infection, surgery is the only treatment proven to help. The risk of death with antibiotic treatment alone is very high, compared with 25% when antibiotics and emergency surgery are used together [25,26,30]. When present, treatment of associated organ failures in the intensive care unit is mandatory. Patients need to stay in the intensive care unit, may require a breathing tube, and usually need more than one operation for the infection to definitively be controlled. The incision in the skin is left open and packed with dressings. Treatment and recovery may take several weeks. Once the infection is definitively cured, patients might need plastic and reconstructive surgery in the areas that were affected. The value of other adjunctive measures (hyperbaric oxygen therapy, intravenous immunoglobulins) is uncertain [26,30,31]. Only an aggressive approach offers the possibility to save limbs (and life) of the affected patients [18,31].

Taking care of pharmacokinetic/pharmacodynamics (PK/PD) principles deriving from the most recent findings may help clinicians in maximizing treatment of SSTI with antimicrobials in every situation [32]. Recent studies suggest that distinguishing between bacteriostatic or bactericidal activity when choosing an antimicrobial for the treatment of severe SSTI could probably be clinically irrelevant. Conversely, what could help clinicians in maximizing the therapeutic efficacy of the various drugs in routine practice is taking care of some PK/PD parameters. Antibiotic therapy for NSTI patients faces several challenges and should achieve the best possible tissue diffusion with regards to impaired regional perfusion, tissue necrosis, and PK/PD alterations [33]. Concentration-dependent agents may exhibit more rapid bacterial killing than observed with time-dependent agents. Serum concentrations may not always adequately predict tissue exposure in patients with SSTIs, and measuring concentrations at the infection site is preferable. Hydrophilic antimicrobials showed generally lower penetration rates than the lipophilic

ones into the interstitial fluids of soft tissue and might require alternative dosing approaches in the presence of severe sepsis or septic shock. Features of septic shock from any cause (increased distribution volume, altered renal clearance, hypoalbuminemia, and reduced tissue perfusion) abound for optimizing delivery of hydrophilic and time-dependent drugs such as β-lactams by using high-loading doses and prolonged infusion with therapeutic drug monitoring [34]. Conversely, tissue penetration of lipophilic antimicrobials, molecules with higher tissue diffusion (e.g., clindamycin, linezolid and daptomycin), is less affected by the pathophysiological status and might be of interest in this setting. Estimation of the probability of target attainment at the infection site is of paramount importance in understanding whether or not the defined daily dosage of a specific antimicrobial may ensure optimal antimicrobial treatment in deep seated infections. Real-time therapeutic drug monitoring may be a very helpful tool for optimizing therapy of severe SSTIs.

Toxin production plays a key role in the pathogenesis of various SSTI caused by Gram-positive bacteria, mainly severe infections by *S. aureus*, *S. pyogenes* or *Clostridium. perfringens*. In standard clinical practice, combined antibiotic treatment is used to treat severe SSTI, whereby one of the drugs is usually a protein synthesis inhibitor antibiotic. These antibiotics given as adjuvant treatment may improve clinical outcomes and survival in patients with severe SSTI. This has been confirmed in *in vitro* studies, animal models, case reports and in clinical patient management. Although randomized clinical trials are lacking, in the light of several new drugs marketed for the treatment of these infections (oxazolidinones, lipoglycopeptides), the data available point to the greater efficacy of these options. Therefore, combination therapy (with β-lactam antibiotics), including an adjuvant protein synthesis inhibitor antibiotic for toxin suppression, should be used both in patients with severe SSTI and in those with moderate infection and risk factors for methicillin-resistant positive- or Panton-Valentine leukocidin positive-*S. aureus* infection [35].

ANTIMICROBIAL TREATMENT OPTIONS AND CONTINUITY OF CARE MANAGEMENT

The selection of initial antimicrobial therapy constitutes a growing challenge in hospitalized patients with cSSTI due to the wide spectrum of pathogens and resistance phenotypes of MDRB that may be encountered [29,36]. In this population, inadequate initial antimicrobial therapy has been associated with longer treatment duration, extended hospitalization, higher healthcare costs, more frequent subsequent readmissions, and an overall increase in the likelihood of death [37]. This issue, which applies to both community-acquired and healthcare associated SSTI, is even more critical in immunocompromised hosts, a subgroup in whom mycobacterial and fungal pathogens may also be implicated [38]. Microbiological documentation is pivotal in moderate-to-severe cases, both for ensuring timely treatment optimization and easing antimicrobial stewardship initiatives to limit unnecessary exposure to broad-spectrum drugs and their inherent adverse events. SSTI management guidelines do not include a clear recommendation on when and how to investigate the cause of SSTI [39]. It is not usually necessary to obtain microbiological samples in uncomplicated infections, except in cases of recurrences or for epidemiological control purposes. In the case of complicated infections, the samples are of two different types: those obtained from the affected area (surgical samples, punctures of abscesses or swabs) and systemic samples (i.e. blood cultures). The clinical condition also determines the type of samples to be obtained. In cases of systemic involvement, blood cultures are mandatory [40]. For immunocompromised patients, who may present atypical infections, detection of antigens, serologies or molecular biology techniques may be helpful. The rapid diagnosis is currently the goal to be pursued by implementing techniques such as matrix assisted laser desorption ionization-time of flight, commercial real-time PCR or the promising next-generation sequencing methods. Rapid diagnostic tools and clinical metagenomics are under evaluation for the management of SSTI and will hopefully help tailoring antimicrobial therapy in a close future in patients with risk factors for MDRB [29,41]. Identifying the optimal empirical antimicrobial regimen in patients with SSTI is increasingly challenging due to the rising prevalence of MDRB as the causative pathogens of these infections and (more generally) the growing population of individuals at-risk for MDRB-related condition.

The mainstem of empiric antibiotic treatment suggested in severe SSTI or in NSTI (and even at probable risk of MDRB) is a broad-spectrum β-lactam (e.g., piperacillin-tazobactam or combination of cephalosporins with new β-lactamase inhibitors) with additional aminoglycosides in case of septic shock33. Clindamycin or linezolid (antibiotics that inhibit protein synthesis) should be included in association in case of documented or suspected *S. pyogenes* infection (limb infection, features of STSS, absence of comorbidities, blunt trauma, absence of chronic skin lesions, homelessness, injectable drug use, non-steroidal anti-inflammatory drug use) or suspicion of MRSA. Coverage of resistant gram-negative bacilli by carbapenems should be used according to local ecology and individual risk factors (hospital acquired infection, β-lactam or quinolone exposure in the previous three months, history of extended spectrum beta-lactamase [ESBL] carrying, germ colonization/infection or travel to high ESBL endemic areas in the previous three months). Similarly, use of anti-MRSA drugs (rare and occasionally against enterococci) such as vancomycin, linezolid, tedizolid or daptomycin should be considered in case of local endemicity, residence in a long-stay care facility, chronic dialysis, permanent transcutaneous medical devices or prior MRSA infection/colonization. MRSA and *P. aeruginosa* represent the main pitfalls that predispose to inadequate initial therapy in community onset SSTI. In patients with hospital-acquired SSTI, MRSA (both hospital-associated and community associated lineages), multi-drug-resistant *P. aeruginosa* and *Acinetobacter baumannii*, ESBL-producing Enterobacterales and vancomycin-resistant enterococci are nowadays isolated on a regular basis, though the risk correlates closely with local epidemiology [29].

Table 3 **Potentially relevant factors to be balanced on a case-by-case basis for optimizing the use of antibiotics (either already available or future new-generation) in patients with SSTI at moderate or high risk of MRSA infection**

Antibiotic	Switch to oral therapy and early discharge	Useful if poor adherence factors to outpatient therapy (oral treatment at home)	Avoidance (no need) of hospitalization	Significant Drug interactions	Use in kidney dysfunction or renal failure	Coverage of GNB	Low risk of CDI	Use if Allergy to β-lactams
New anti-MRSA cephalosporins: Ceftaroline, Ceftobiprole	-	-	-	-	(+)*	+	-	-
Tedizolid	+	-	+	+	+	-	+	+
Long-acting lipoglycopeptides: Dalbavancin, Oritavancin	-	+	+	-	(+/-)*	-	+	+
Telavancin	-	-	-	-	-	-	+	+
Delafloxacin	+	-	+	(-)*	(+/-)*	+	-	+
Omadacycline	+	-	+	+	+	+	-	+

Skin and soft tissue infections (SSTI); methicillin-resistant *Staphylococcus aureus* (MRSA); *Clostridioides difficile* infection (CDI); Gram-negative bacilli (GNB). (+)*: Dosage adjustments adapted to creatinine clearance are necessary. (-)*: Less common and relevant than in older quinolones. (+/-)*: Still with little experience and few data.

There are now several active agents against MRSA and other gram-positive cocci that are FDA-approved for the treatment of SSTI [23], including tedizolid [42], ceftaroline, ceftobiprole [43], delafloxacin (an anionic fluoroquinolone) [44], new long half-life glycopeptides (dalbavancin, oritavancin) [45,46], telavancin and omadacycline (based on an aminomethylcycline) [47] [these last two not yet in Spain] [48]. Considering the similar efficacy that arose from direct comparisons in phase-3 randomized clinical trials to ABSSSI, in order to adopt the best approach for treating cSSTI on patient-tailored basis, the different safety profiles and formulations of the different available agents should be balanced by taking into account the specific features of each treated patient in terms of baseline comorbidities, related risk of toxicity, need for hospitalization, possibility of early discharge, and expected adherence to outpatient oral therapy. Ceftaroline, ceftobiprole, dalbavancin, oritavancin and telavancin are intravenous antibiotics offering excellent coverage for MRSA-SSTI and either expanded spectrum, longer half-life or better safety profile than older formulations. Delafloxacin, omadacycline and tedizolid are new oral antibiotics for treatment of SSTI with available intravenous formulations, making them potential step-down therapies. In turn, delafloxacin and omadacycline have expanded spectrum of coverage with activity against Gram-negative pathogens, making them attractive options for empiric treatment [49]. Older treatment options may be associated with toxicity and require frequent dosing; however, the current IDSA guidelines for MRSA infection and SSTI [17] as well as the recently published UK guidelines [50] on MRSA treatment only consider these drugs as alternative choices or do not mention them at all [48].

Current and future options for treating cSSTI focus on fluoroquinolones and long-acting lipoglycopeptide antibiotics. Clinical and pharmacological characteristics, advantages and limitations of the fourth-generation fluoroquinolone –delafloxacin-, and the semisynthetic long-acting lipoglycopeptide agents –dalbavancin and oritavancin- have been reviewed in detail in recent publications [44,45,46,48,49,51]. Delafloxacin is an anionic fluoroquinolone, active at acid pH (e.g. cystic fibrosis, abscesses or skin necrosis), with excellent penetration into biofilms, high potency against pneumococci, streptococci and staphylococci, as well as being active on MDRB strains and isolates resistant to levo/moxifloxacin. Its current approved indications are cSSTI, community-acquired pneumonia, and would allow sequential treatment from iv. to oral route [43,50]. Dalbavancin and oritavancin are characterized by the presence of an additional hydrophobic moiety, which determine their long half-lives (terminal half-life of 336 and 393 hours, respectively) but, most importantly, markedly improve their antimicrobial activity by increasing their membrane affinity and thus their concentration near the target [23,45,46,48,49,51]. Long-acting lipoglycopeptide antimicrobials represent another strategy for achieving ED. Their long half-lives allow treatment of SSTI with a single or weekly iv. dose, providing long-term iv. treatment without requiring continuous iv. access or inpatient stay. While they are approved by the FDA for SSTI / ABSSSI, their pharmacological properties suggest a potential role for the treatment of deep-seated and severe infections, such as bloodstream and bone and joint infections.

Both families of antibiotics could achieve: a) A reduction in hospital admissions; b) A shortening of the length of hospital stays; c) Easiness of early discharge; d) Maintenance of

high quality of care; and e) Adherence to antimicrobial stewardship.

So, for this reason, the use of these antimicrobials is particularly appealing when prolonged therapy, early discharge, suspicion of poor or non-adherence to oral therapy and avoidance of long-term intravascular catheter access are desirable or when multidrug-resistant bacteria are suspected. Other factors to be taken into account for influencing the choice when considering novel, approved agents for the treatment of cSSTI, especially in patients at high risk of MRSA infection (Table 2), are: acute kidney injury or chronic kidney disease, reduced platelet count or concomitant selective serotonin reuptake inhibitors, risk of *Clostridioides difficile* infection, no (more) need for hospitalization or facilitate switch to oral and early discharge possible (Table 3).

CONCLUSIONS

With the development of new drugs and the current evidence of their use, there is a need to refine the appropriate drug's decision-making. Drugs with a long half-life (long-acting lipoglycopeptides such as dalbavancin, oritavancin), which allows weekly administration (or even greater), can reduce hospital admission and length of stay with fewer healthcare resources through outpatient management (home hospitalization or day hospitals). New anionic fluoroquinolones (e.g. delafloxacin) that are highly active in an acidic medium and have a great capacity for tissue penetration, with a greater safety profile and the possibility of switch from the intravenous to the oral route, will also make it possible to achieve these new healthcare goals and promote continuity of care. Shorter courses of antibiotics are recommended based on the doctrine of "less is more", backed by scientific evidence.

Careful evaluation of antibiotic therapy after 48-72 h of initial therapy could help clinicians in early identification of patients with treatment failure and, therefore, consider an alternative approach or a new surgical or instrumental revision in "focus control". Surgery is an essential part of managing many SSTIs, but guidelines often do not include clear indications for either timing or surgical technique. Close monitoring of patients with multiple comorbidities, drug-drug interaction or adverse host factors are also necessary. In cSSTI or NSTI, PK/PD should be optimized by use of high-loading doses and prolonged infusions for molecules with time-dependent bactericidal activity such as β-lactams, and therapeutic drug monitoring should be used when available. The role of stewardship programs will continue to expand, but the positioning of oral antimicrobials in treating severe SSTI requiring hospitalization is unclear, as is the timing and manner of de-escalation of intravenous treatments.

Therefore, management should rely on a collaborative multidisciplinary group with experience in this infectious syndrome.

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Clinical approach

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Treatment guidelines for multidrug-resistant Gram-negative microorganisms

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ABSTRACT

In recent years, new antimicrobials have been introduced in therapeutics, including new beta-lactam-beta-lactamase inhibitor combinations and cefiderocol in response to therapeutic needs in the face of increasing resistance. There are also different treatment guidelines for infections caused by these microorganisms that have been approved by different professional societies, including those of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Disease Society of America (IDSA) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). All of them are based on scientific evidence, but with differences in the weight of expert opinion in their recommendations. Both ESCMID and IDSA include recommendations for the treatment of extended-spectrum beta-lactamase-producing microorganisms. The IDSA is the only one including AmpC producers, all address the treatment of infections caused by carbapenem-resistant Enterobacterales and *Acinetobacter baumannii* and multidrug-resistant or difficult-to-treat *Pseudomonas aeruginosa*, and the IDSA and SEIMC include recommendations on the treatment of *Stenotrophomonas maltophilia*. Future guidelines should integrate new antimicrobials and new innovative management options not covered by current guidelines.

Keywords: multidrug resistant Gram-negatives, guidelines, beta-lactam-beta-lactamase inhibitor combinations, cefiderocol.

INTRODUCTION

The emergence of different resistance mechanisms affecting antimicrobials in recent years has significantly complicated the treatment of infectious diseases [1]. This fact has been reflected in the latest guidelines published on the treatment of infections caused by multidrug-resistant (MDR) gram-negative microorganisms. These guidelines include those agreed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Disease Society of America (IDSA) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) [2-5]. One of the resistance mechanisms on which these guidelines have focused their attention is that due to the production of carbapenemases associated with mobile genetic elements. They have been described mainly in Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [6]. In this paper we briefly analyse their description, the initial approaches for the treatment of infection due to microorganisms expressing the acquired carbapenemases prior to the introduction of beta-lactam/beta-lactamase inhibitor combinations and cefiderocol, and the similarities and differences between current treatment guidelines.

TEMPORAL DESCRIPTION OF EXTENDED SPECTRUM BETA-LACTAMASES, PLASMID AMPC BETA-LACTAMASES AND CARBAPENEMASES

The successive emergence and spread of beta-lactamases, the main resistance mechanism affecting beta-lactam antibiotics in Gram-negative bacteria, has complicated the treatment of infections caused by these microorganisms, only partly mitigated by the succeeding introduction of new antimicrobials [7].

Extended spectrum beta-lactamases (ESBLs) were first described in 1983 as mutant derivatives from TEM-1 (Temoneira class A extended-spectrum β-lactamase), TEM-2 and SHV-1 (sulfhydryl variant of the TEM enzyme). They are character-

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ized for their hydrolytic activity of extended spectrum cephalosporins and aztreonam but not to methoxy-beta-lactams (temocillin and cefoxitin) and carbapenems. They are inhibited by clavulanic acid, sulbactam and tazobactam and also by the new beta-lactamase inhibitors (avibactam, varbobactam and relebactam). Later in 1991, CTX-M-1 (cefotaxime-hydrolyzing β-lactamase-Munich) ESBL were described. This enzyme inaugurates the family currently dominating the landscape of ESBLs all over the world, being plasmid derivatives of chromosomally encoded enzymes in *Kluyvera* spp. and mainly found in Enterobacterales [8].

The first report demonstrating that a chromosomal AmpC beta-lactamase (ampicillin chromosomal cephalosporinase) gene can be capture by a plasmid was performed in 1990. The report described transmissible resistance to methoxy- and oxyimino-beta-lactams mediated by the MIR-1 (Miriam Hospital) enzyme with the biochemical properties of a chromosomal AmpC beta-lactamase, showing that the bla_{MIR-1} gene was 90% identical to the bla_{AmpC} gene of *Enterobacter cloacae* [9]. This report inaugurates the description of several plasmid AmpC enzymes, also mainly described in Enterobacterales.

However, with current antimicrobial armamentarium, acquired carbapenemases are the resistance mechanisms that most complicate prescribing old and new antimicrobials. They confer resistance to nearly all beta-lactams and isolates expressing carbapenemases also harbour resistance determinants to other antimicrobials such as aminoglycosides and/or fluoroquinolones [1]. Plasmid mediated carbapenemases were first described in *P. aeruginosa* in Japan in 1991, with IMP-1 (Imipenemase), a metallo-beta-lactamase or class B carbapenemase that was later found in different species of Enterobacterales. In 1996, class A carbapenemase, KPC-1 (*Klebsiella* producing carbapenemase) was recognized for the first time in the United States in an isolate of *Klebsiella pneumoniae*. In 1988 GES-1 (Guyana extended spectrum) enzyme, initially described as an ESBL, inaugurates this family with latter variants acquiring hydrolytic capacity against carbapenems. They are currently more relevant in *P. aeruginosa* but also in Enterobacterales [10]. In 2001, VIM-type metallo-beta-lactamases (Verone integron-encoded metallo-β-lactamase) were described in *P. aeruginosa* in Italy, in 2003 the class D carbapenemases derived from OXA-48 (oxacillin carbapenemase/oxacillinase) in Turkey in *K. pneumoniae*, and in 2008 NDM-1 (New Deli metallo-beta-lactamase) in Sweden in an infection due to a *K. pneumoniae* in a patient transferred from India [6].

In *A. baumannii*, acquired carbapenemases are dominated by OXA-23 and their derivatives and by the acquisition of NDM-1 metallo-beta-lactamase [11]. OXA-23 carbapenemase, widely distributed worldwide, was initially described as ARI-1. It was found in an *A. baumannii* isolate in 1985 in Scotland. Other relevant acquired carbapenemases are OXA-24, -51, -58, -134 and -143 demonstrating the facility of this microorganisms to capture resistance genes.

ANTIMICROBIAL TREATMENT PRIOR TO THE INTRODUCTION OF BETA-LACTAM/BETA-LACTAMASE INHIBITOR COMBINATIONS AND CEFIDEROCOL

The dispersion of the aforementioned enzymes and the absence of specific inhibitors of carbapenemases before their introduction in therapeutics made the treatment of infections in which carbapenemase-producing microorganisms were present extremely complicated. This situation was aggravated by the presence of other resistance mechanisms involving aminoglycosides or fluoroquinolones in these microorganisms. As treatment strategies, including in countries with limited access to new antimicrobials, the use of broad-spectrum beta-lactams was recommended despite the production of carbapenemase. The carbapenems with optimized treatment regimens were mostly used [12]. This recommendation was based on the use of high doses of meropenem (2 g every 8 hours) with extended perfusion time (3-4 hours) to improve the PK/PD parameter of time above the minimum inhibitory concentration (MIC). Both *in vitro* studies with killing curves and animal studies supported this recommendation. It was also sustained by the results observed in patients, with greater benefit being achieved by associating carbapenems (essentially meropenem) with antibiotics for which susceptibility had previously been demonstrated [12]. These antibiotics were colistin, aminoglycosides, fluoroquinolones, fosfomycin or tigecycline. Optimization of the use of carbapenems and improvement of the PK/PD parameter is briefly described in the rational documents on the EUCAST website (https://www.eucast.org/publications-and-documents/rd). Moreover, for metallo-beta-lactamase producing microorganisms the use of aztreonam were also recommended as this compound is not hydrolyzed by some of these enzymes [13]. Nevertheless, in many cases it uses was limited by the simultaneous production of an ESBL that affect aztreonam.

CURRENT TREATMENT GUIDELINES FOR MULTIDRUG-RESISTANT GRAM-NEGATIVE MICROORGANISMS

The similarities and differences in the methodology used in the different guidelines are shown in table 1, as well as their contents. Both the ESCMID and SEIMC guidelines were established performing a systematic review of the literature. In the first case, the recommendations were strictly classified using the GRADE methodology, while in the SEIMC guideline they were classified using the IDSA recommendations with the addition of expert opinions. In the case of the IDSA, the literature review was not strictly systematic and the recommendations were based on similar criteria to those of the SEIMC but with a greater weight on the expert opinion [2-5].

In terms of content, both ESCMID and IDSA include recommendations on the treatment of ESBL-producing microorganisms, while IDSA is the only one that includes AmpC producers. In contrast, they all address the treatment of car-

Table 1 **Current guidelines from different societies in the management of infections due to multidrug-resistant gram-negative microorganisms**

	ESCMID	IDSA	SEIMC
Date of publication	16 December 2021	31 March 2022 / 3 July 2022	28 July 2022
Methodology	Literature systematic review with evidence classified with GRADE	Literature nonsystematic review + panellist's clinical experience	Literature systematic critical review with evidence classified with IDSA quality standards + panelist's expert opinion
3rd gen. cephalosporin resistant (ESBL) Enterobacterales	√	√	-
Chromosomal inducible and plasmid AmpC Enterobacterales	-	√	-
Carbapenem-resistant Enterobacterales	√	√	√
Difficult to treat *Pseudomonas aeruginosa*	√	√	√
Carbapenem-resistant *Acinetobacter baumannii*	√	√	√
Stenotrophomonas maltophilia	-	√	√

ESBL: extended spectrum beta-lactamase

bapenem-resistant Enterobacterales and *A. baumannii* and MDR or difficult-to-treat (DTR) *P. aeruginosa* (2,3). Finally, the IDSA and the SEIMC guidelines include recommendations on the treatment of *Stenotrophomonas maltophilia* (2-4).

Treatment of extended-spectrum beta-lactam-producing Enterobacterales (ESCMID and IDSA guidelines). Empirical treatment of ESBL producing Enterobacterales is not addressed in any of the ESCMID and IDSA guidelines [2-4]. They only established targeted recommendations. In case of severe infections, the use of carbapenems (meropenem and imipenem, or ertapenem, the last one only in the absence of septic shock) is preferred over penicillin combinations with beta-lactamase inhibitors (piperacillin-tazobactam or amoxicillin-clavulanic acid). In both cases, these recommendations are supported by the results of the Merino trial and *in vitro* susceptibility data [14]. Both also contain recommendations to minimise the use of carbapenems to avoid selective pressure on carbapenemase-producing microorganisms. ESCMID recommend the use of piperacillin-tazobactam or amoxicillin-clavulanate in low-risk patients or in patients with non-severe infections or also together with quinolones and co-trimoxazole as step-down therapy once the susceptibility profile is known. For this situation, the IDSA only recommends quinolones and co-trimoxazole.

Both guidelines address urinary tract infections (UTI) due to ESBL producing Enterobacterales. In ESCMID guidelines, aminoglycosides or fosfomycin (i.v.) are recommended for complicated UTI (cUTI) without septic shock. The IDSA only specifically addresses uncomplicated UTI (uUTI), recommending the use of nitrofurantoin, co-trimoxazole, oral fosfomycin, aminoglycoside (single dose) or piperacillin-tazobactam. Both guidelines agree to avoid the use of new beta-lactam/beta-lactamase inhibitor combinations or cefepime, except in cystitis with clinical improvement. The use of tigecyline in not recommended due to poor urinary elimination.

Treatment of AmpC producing Enterobacterales (IDSA guidelines). IDSA guidelines are the only one that includes recommendations for the treatment of AmpC producing Enterobacterales [3]. They are stratified regarding the risk for clinically significant AmpC production and microorganism. *Serratia marcescens, Morganella morganii* and *Providencia* spp. are considered at low-risk and treatment should be selected according to the susceptibility testing results.

For *Enterobacter cloacae, Klebsiella aerogenes* and *Citrobacter freundii*, considered as moderate- to high-risk, recommendations include to avoid piperacillin/tazobactam, ceftriaxone (also cefotaxime) or ceftazidime, even if tested susceptible *in vitro* (except in uUTI). Cefepime is recommended if MIC values are lower than 2 mg/L (even if ceftriaxone is tested *in vitro* susceptible). In this guideline, the carbapenems are aloud when cefepime MICs are higher or equal of 4 mg/L. Moreover, they recommend not to use new beta-lactam/beta-lactamase inhibitors combinations (ceftazidime/avibactam or ceftolozane/tazobactam) or cefiderocol and to reserve them for carbapenemase producers. Also, co-trimoxazole or fluoroquinolones are recommended if tested *in vitro* susceptible and nitrofurantoin in uUTI if tested *in vitro* susceptible. Unfortunately, the IDSA guidelines do not include specific recommendations for infections due to microorganisms with plasmid AmpC enzymes. However, with current knowledge, recommendations can be similar of that performed for *E. cloacae, K. aerogenes* and *C. freundii* [15].

Treatment of carbapenemase producing Enterobacterales (ESCMID, IDSA and SEIMC guidelines). Current recommendations of all three guidelines for the treatment of car-

Table 2 **Summary of recommendations in the ESCMID, IDSA and SEIMC guidelines for the treatment of infections due to carbapenemase producing Enterobacterales. Dosages of the different antimicrobials are those included in the Summary of Product Characteristics (SmPC).**

Society Year of publication	Carbapenemase type KPC	 OXA-48	 MBL
ESCMID 2021	Ceftazidime-avibactam* Meropenem-vaborbactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	Non-severe infection: Aminoglycosides (UTI) or tigecycline (not in bacteraemia /pneumonia)		
IDSA 2022	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-relebactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	UTI → Aminoglycosides, cefiderocol, meropenem Abdominal → Tigecycline, eravacycline		
SEIMC 2022	Ceftazidime-avibactam Meropenem-vaborbactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	Alternative → Combined therapy (meropenem, colistin, tigecycline, aminoglycosides...)		

UTI: urinary tract infection.

bapenemase producing Enterobacterales pivot on the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol [2,4,5]. Table 2 summarized these recommendations according to different carbapenemases. For systemic infections, all of them agree on the use of cetazidime-avibactam or meropenem-vaborbactam just for KPC producers and IDSA also mention imipenem-relebactam. Moreover, all also agree on the use of ceftazidime/avibactam for OXA-48 producers and in combination with aztreonam for metallo-beta-lactamase producers. For the latest, cefiderocol is also mentioned.

Alternatively, for non-severe infections ESCMID guidelines recommend the use of aminoglycosides in UTI or tigecycline in infections other than bacteraemia and pneumonia due to low favourable PK/PD parameter in these infections. IDSA guidelines also recommend aminoglycosides in UTI as well as cefiderocol and meropenem and for intraabdominal infections, tigecycline and eravacycline. Lastly, SEIMC guidelines includes alternatively meropenem, colistin, tigecycline, or aminoglycosides guided by in vitro susceptibility and/or local epidemiology.

All three guidelines also specifically address UTIs. ESCMID guidelines mention cUTI and recommend aminoglycosides, particularly plazomycin despite this drug in not currently marketed, co-trimoxazole and intravenous fosfomycin. IDSA differentiates cystitis and cUTI and pyelonephritis. For cystitis several antimicrobials are recommended and include fluoroquinolones (ciprofloxacin or levofloxacin), co-trimoxazole, nitrofurantoin, single dose of an aminoglycoside and meropenem or colistin as an alternative. For cUTI and pyelonephritis, meropenem high dose as first choice or an aminoglycoside as an alternative. SEIMC differentiated low- and high-risk patients. For the former, first line recommendation is an aminoglycoside or co-trimoxazole and as an alternative similar recommendation than IDSA plus fosfomycin. In high-risk patients the antimicrobials are an aminoglycoside and fosfomycin.

Treatment of multi-drug resistant/difficult to treat *Pseudomonas aeruginosa* (ESCMID, IDSA and SEIMC guidelines). All guidelines stratified recommendations according to the patients (low-risk or non-severe and severe) or when combination therapy is needed [2-5] (Table 3). For low-risk or non-severe, ESCMID is the most conservative with old antibiotics if tested *in vitro* susceptible. IDSA includes new antimicrobials (ceftolozane-tazobactam, imipenem-relebactam, ceftazidime-avibactam) or a single dose of an aminoglycoside for uUTI. SEIMC preferred recommendation is ceftolozane-tazobactam and as an alternative ceftazidime-avibactam or cefiderocol. For severe cases, ESCMID only recommends ceftolozane-tazobactam and IDSA on top of this combination also imipenem-relebactam, ceftazidime-avibactam and cefiderocol in cUTI. SEIMC preferred recommendation is ceftolozane-tazobactam and as an alternative ceftazidime-avibactam, imipenem-relebactam, colistin or cefiderocol.

ESCMID and IDSA do not routinely recommended combination therapy but if used, it should be based in two *in vitro* active antibiotics. Nevertheless, if preferred regimen has no *in vitro* activity it should be combined with an aminoglycoside. SEIMC only recommends combination therapy in severe infections and those with high inoculum to avoid risk of developing resistance mechanism. Recommendations includes ceftolozane-tazobactam or ceftazidime-avibactam with an active aminoglycoside or colistin, fosfomycin if MIC values are lower than 128 mg/L with an active compound. Moreover, rifampicin should be avoided even in combination.

Carbapenem resistant *Acinetobacter baumannii* (ESCMID, IDSA and SEIMC guidelines)

Carbapenem resistance in *A. baumannii* is currently due to

Table 3 **Summary of recommendations in the ESCMID, IDSA and SEIMC guidelines for the treatment of infections due to multi-drug resistant/difficult to treat *Pseudomonas aeruginosa*. Dosages of the different antimicrobials are those included in the Summary of Product Characteristics (SmPC).**

Infection type /combination therapy	ESCMID	IDSA	SEIMC
Low-risk, non-severe	Old antibiotics with in vitro activity	Ceftolozane-tazobactam or imipenem-relebactam or ceftazidime-avibactam or single dose aminoglycoside (uUTI)	Preferred: Ceftolozane-tazobactam Alternative: Ceftazidime-avibactam, or cefiderocol (uUTI)
Severe	Ceftolozane-tazobactam cefiderocol (cUTI)	Ceftolozane-tazobactam or imipenem-relebactam or ceftazidime-avibactam or cefiderocol (cUTI)	Preferred: Ceftolozane-tazobactam Alternative: Ceftazidime avibactam, imipenem-relebactam or colistin
Combination therapy	Not routinely recommended but if used, select two active antibiotics	Not routinely recommended but if preferred regimen has no in vitro activity combine with an aminoglycoside	Only in severe infections and those with high inoculum: - Ceftolozane-tazobactam or ceftazidime-avibactam with an active aminoglycoside or colistin - Fosfomycin (<128 mg/L) with an active compound - Avoid rifampicin, even in combination

uUTI: uncomplicated urinary tract infection; CUTI: complicated urinary tract infection

OXA carbapenemases, mainly OXA-23 and its derivatives, and to a lesser extent metallo-beta-lactamases, mainly NDM and VIM derivatives [11]. Recommendations are classified regarding infection type and *in vitro* susceptibility of ampicillin-sulbactam. This recommendation is base in the intrinsic activity of sulbactam alone but tested in combination with ampicillin. In mild to moderate infections, if *A. baumannii* tested ampicillin-sulbactam susceptible, this is the first option in all guidelines with colistin as an alternative [3-5]. Nevertheless, all of them include other alternatives such as tigecycline high dose in ESCMID guidelines, minocycline and cefiderocol (refractory to other antibiotics) in IDSA guidelines and ampicillin-sulbactam high dose in combination with colistin or aminoglycosides or minocycline or tygecycline high dose in SEIMC guidelines.

In mild to moderate infections due to ampicillin-resistant *A. baumannii* there are relevant differences between different guidelines. ESCMID recommend polymyxins or tigecycline with high dose, IDSA recommend ampicillin-sulbactam high dose in combination with a second active agent and SEIMC recommend cefiderocol in combination with colistin or a triple therapy in pan-drug resistant isolates.

In severe infections, all guidelines recommend combination therapy with two active agents but with specific remarks. ESCMID recommend to avoid polymyxin-meropenem or polymyxin-rifampicin combinations, IDSA recommend to avoid rifampicin, fosfomycin in any combination and polymyxin-meropenem without a third (active) agent and SEIMC recommend cefiderocol (as part of combination) but avoiding rifampicin.

It is of note that none of the guidelines include new beta-lactam beta-lactamase inhibitor combinations in their recommendations due to the absence of inhibitory activity of the current inhibitors to carbapenemases that are actually present in *A. baumannii* [11]. One exception could be when KPC carbapenemases are present, in which meropenem-varbobactam or imipenem-relebactam might be useful. Nevertheless, this situation is currently rare from an epidemiological point of view.

Stenotrophomonas maltophilia (IDSA and SEIMC guidelines)

S. maltophilia is intrinsically resistant to several antimicrobials, including beta-lactams and aminoglycosides. IDSA and SEIMC guidelines include recommendations for infections due to this pathogen [3]. For mild infection, preferred treatment is co-trimoxazole and minocycline in monotherapy and as an alternative tigecycline, levofloxacin or cefiderocol in monotherapy. Expressly advises to avoid the use of ceftazidime.

For moderate to severe infection at least three different approaches are recommended: i) combination of co-trimoxazole plus minocycline, ii) initiation of co-trimoxazole in monotherapy with latter addition of minocycline (preferred), tigecycline, levofloxacin or cefiderocol if there is a delay in clinical improvement with co-trimoxazole alone and iii) ceftazidime-avibactam plus aztreonam, when intolerance or inactivity of other agents are anticipated.

FUTURE CHALLENGES

There are several challenges that should be addressed in the near future as epidemiology of different resistant mechanisms that impact in the selection of antimicrobial agents is rapidly changing and new antimicrobial do no cover all the expectation [7]. Among these challenges we can enumerate the

presence of MDR pathogens in extrahospitalary patients, in nursing homes and in long-term care facilities, the increased description of isolates with more than one carbapenemase, the implementation of new strategies for the reimbursement of new antimicrobials and future new antimicrobials such as gepotidacin and new combinations such as cefepime-taniborbactam, cefepime-zidebactam, cefepime-enmetazobactam, ceftaroline-avibactam, aztreonam-avibactam, ceftibuten-avibactam, sulbactam-durlobactam that should integrate in the guidelines. Moreover, the introduction of new diagnostic techniques or potentially new (therapeutic) strategies such as fecal microbiota transference, the use of phages and endolysins or gene editing (CRISPR.Cas) should be also positioning in the management of infections due to MDR pathogens.

CONFLICT OF INTEREST

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Post-CART-T Cell Infection: Etiology, pathogenesis, and therapeutic approaches

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ABSTRACT

Chimeric antigen receptor (CAR) T cell therapy targeting CD-19 has revolutionized the treatment of refractory B-cell malignancies. However, patients undergoing this therapy face an increased risk of infections due to compromised immune function, lymphodepleting chemotherapy, hospitalization, and therapy-related complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome. Patients with systemic corticosteroid use, low immunoglobulin levels, and severe CRS, are at higher risk of infection. This review article highlights the spectrum of infections encountered in CAR T cell therapy, including bacterial, viral, and fungal infections. Following consensus guidelines for vaccination and immunoglobulin replacement is recommended. Clear criteria for antibiotic usage and vaccinating household members against respiratory viruses are crucial. Understanding the risk factors, spectrum of infections, and implementing appropriate prophylactic measures are essential to optimize outcomes in patients undergoing CAR T cell therapy. By prioritizing infection prevention strategies, healthcare professionals can effectively improve patient care.

Keywords: CAR T cell therapy, infection, immunoglobulin replacement, vaccination, neutropenia, hypogammaglobulinemia.

THE CONCEPT OF CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

CD-19-targeted chimeric antigen receptor (CAR) T cell therapy is a highly efficacious treatment modality that has exhibited significant advancements in the management of patients diagnosed with refractory B-cell malignancies. By utilizing genetically engineered T cells expressing CARs specific to CD-19, a surface antigen expressed on B cells, this therapy enables precise recognition and elimination of malignant B cells. Through the activation of CAR signalling, engineered T cells are equipped with enhanced cytotoxic potential, leading to improved patient outcomes. The successful implementation of CD-19-targeted CAR T cell therapy has revolutionized the treatment landscape for patients with refractory B-cell malignancies, as evidenced by numerous studies [1,2].

RELATIONSHIP BETWEEN CAR T CELLS AND INFECTION: INSIGHTS AND IMPLICATIONS

Patients undergoing CAR T cell therapy are at increased risk of infection due to various contributing factors [3]. Initially, these patients often exhibit compromised immune function as a result of their underlying malignancy and prior cytotoxic treatments. Additionally, lymphodepleting chemotherapy administered prior to CAR T cell infusion can lead to cytopenias and potential impairment of mucosal barriers. Hospitalization in conventional wards or intensive care units (ICUs) is often necessary for these patients, who may have vascular and/or urinary catheters and may require mechanical ventilation, thereby increasing the likelihood of nosocomial infections. Moreover, CAR T cell therapy can be complicated by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which may require treatment with interleukin-6 inhibitors and corticosteroids depending on the severity of symptoms. The use of immunosuppressors further predisposes these patients to infections [4]. Furthermore, patients undergoing CAR T cell therapy commonly experience prolonged hypogammaglobulinemia, as well as potential long-lasting neutropenia and/or lymphopenia.

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ARE THERE PATIENT SUBGROUPS WITH AN INCREASED SUSCEPTIBILITY TO INFECTION?

There are various studies aiming to identify which patients receiving CAR T-cell therapy are at higher risk of developing an infection. Patients with systemic corticosteroid use, impaired performance status, prior infection before CAR-T infusion, and low IgG levels before lymphodepletion chemotherapy were found to have a higher risk of infection [5-6]. A previous study also reported that patients with severe CRS were more prone to infection [4].

Recently, authors have published a score based on analytical parameters at the time of lymphodepletion to risk-stratify patients for infectious complications and poor survival outcomes prior to CD19 CAR-T therapy [7]. High punctuation in this score (HThigh) has been associated with an increased risk of infection. The authors propose that their score be utilized to define antibacterial prophylaxis strategies.

WHAT INFECTIONS DO THESE PATIENTS HAVE?

These patients can experience bacterial, viral, and fungal infections [3-5]. During the neutropenic phase, patients are predominantly at risk for endogenous bacterial infections associated with neutropenia or healthcare-associated bacterial infections. Fungal infections are most commonly diagnosed during this phase. It is important to highlight the high percentage of patients in this population with *Clostridium difficile* infections. This is correlated with the extensive antibiotic use in this population, as fever is commonly observed following CAR-T infusion. Establishing clear criteria for when these patients require antibiotics is of utmost importance, as well as antibiotics stewardship strategies in order to shorten treatment duration as much as possible when there is no microbiological documentation and the patient is clinically stable.

In a later stage, when patients have recovered from neutropenia, bacterial and viral infections are more frequent. Viral infections, likely related to long-term CAR-T-induced immunological dysfunction, are common. The use of vaccines in this population, and particularly vaccinating household members against respiratory viruses, may be crucial.

HOW CAN THE INFECTIONS BE PREVENTED?

The cornerstone of infection prevention in this population is antibacterial and antifungal prophylaxis during the neutropenic phase, immunoglobulin replacement in cases of severe hypogammaglobulinemia, and vaccination. These authors recommend following the vaccination and immunoglobulin replacement guidelines proposed in the most important consensus documents published to date [3,8].

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CONFLICTS OF INTEREST

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Trends in infectious diseases

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Present and future of resistance in *Pseudomonas aeruginosa*: implications for treatment

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ABSTRACT

Pseudomonas aeruginosa is a pathogen that has a high propensity to develop antibiotic resistance, and the emergence of multidrug-resistant strains is a major concern for global health. The mortality rate associated with infections caused by this microorganism is significant, especially those caused by multidrug-resistant strains. The antibiotics used to treat these infections include quinolones, aminoglycosides, colistin, and β-lactams. However, novel combinations of β-lactams-β-lactamase inhibitors and cefiderocol offer advantages over other members of their family due to their better activity against certain resistance mechanisms.

Selecting the appropriate empiric antibiotic treatment requires consideration of the patient's clinical entity, comorbidities, and risk factors for multidrug-resistant pathogen infections, and local epidemiological data. Optimizing antibiotic pharmacokinetics, controlling the source of infection, and appropriate collection of samples are crucial for successful treatment.

In the future, the development of alternative treatments and strategies, such as antimicrobial peptides, new antibiotics, phage therapy, vaccines, and colonization control, holds great promise for the management of *P. aeruginosa* infections.

Keywords: *Pseudomonas aeruginosa*; antibiotic resistance; Metallo-β-lactamases; Ceftolozane-tazobactam; Ceftazidime-avibactam; Cefiderocol; Imipenem-Relebactam; Meropenem-vaborbactam

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PSEUDOMONAS AERUGINOSA: A VERSATILE PATHOGEN

P. aeruginosa is an extremely versatile pathogen with three key characteristics (Figure 1). Firstly, it has a high adaptive capacity resulting from its ability to generate mutations at a high rate, its genomic plasticity, its ability to form biofilms and enter a *persister* state, and its *quorum* sensing communication mechanisms. Secondly, it has a large arsenal of virulence factors, such as pigments, exotoxins, proteases, secretory systems, and biofilm formation. Thirdly, it has a high potential to generate and transmit antibiotic resistance [1].

This bacterium is responsible for a wide variety of infections at different anatomical levels, but it is important to note two aspects when studying these infections. Firstly, it is primarily considered an opportunistic pathogen, so there are patient-specific criteria that must be met for a P. aeruginosa infection to occur, and the severity of the infection is modulated by factors such as the patient's level of immunosuppression, exposure to medical devices, length of hospital stay, and location in the hospital [1].

Biofilm formation is implicated in infections caused by P. aeruginosa, with classical examples being chronically infected cystic fibrosis or ventilator-associated pneumonia. Hypermutant strains have been described within the biofilm, which may generate and share resistance mechanisms [2].

PSEUDOMONAS AERUGINOSA: THE PARADIGM OF ANTIBIOTIC RESISTANCE

The antibiotic resistance mechanisms of this bacterium can be categorized as innate and acquired. Innate mechanisms, such as low outer membrane permeability, Mex-type efflux pumps, and AmpC cephalosporinase, are common features of this species. Acquired mechanisms can be acquired through

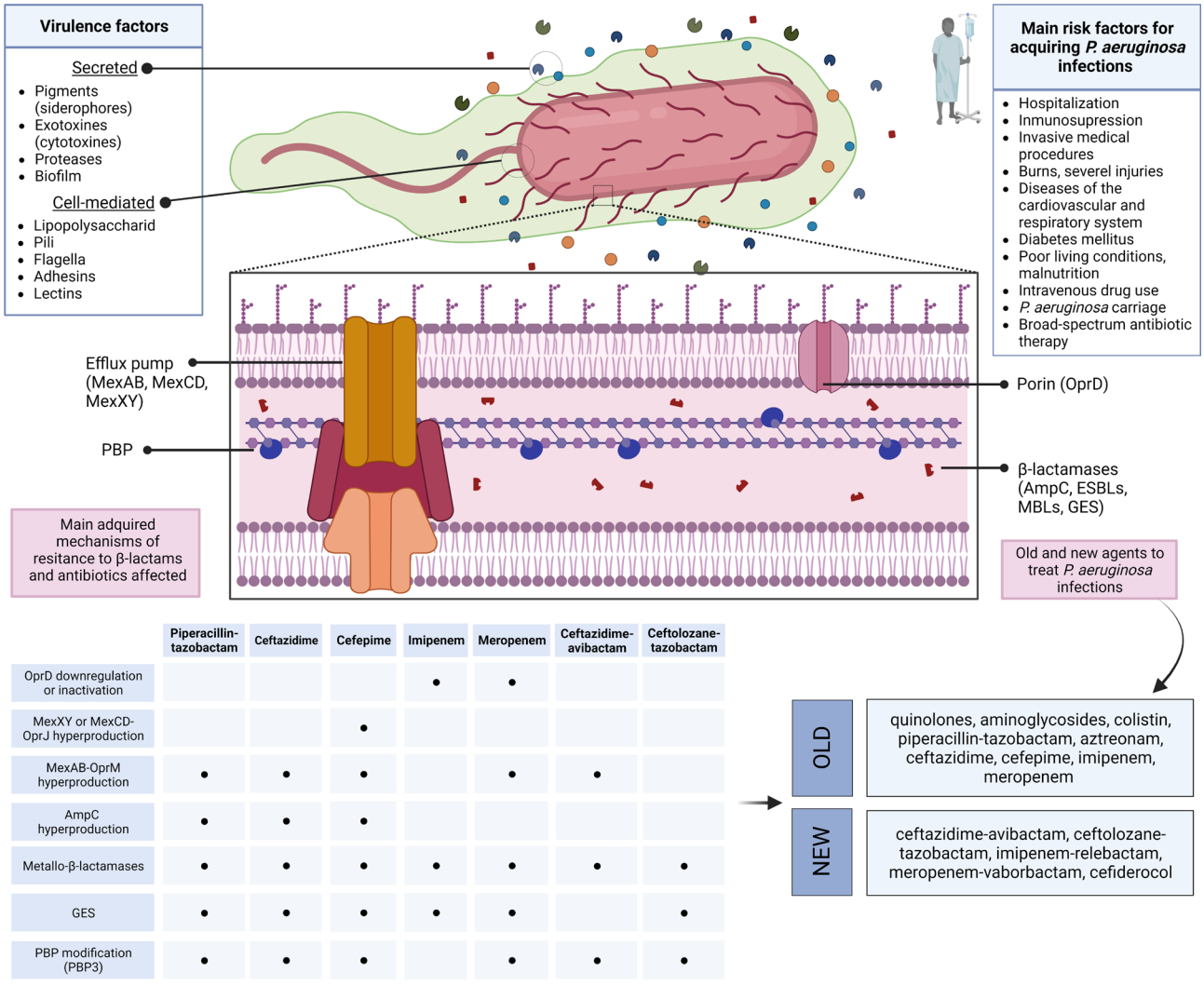

Figure 1 | **Virulence factors, risk factors for acquiring infection, scheme of β-lactam resistance mechanisms and agents to treat *Pseudomonas aeruginosa* infections.**

ESBLs: extended-spectrum β-lactamases, MBLs: metallo-β-lactamases, GES: Guiana extended-spectrum β-lactamase. Created with BioRender.com

chromosomal gene mutations or horizontal transfer. Some of the most frequent mechanisms of acquired resistance through mutations include overproduction of chromosomal AmpC cephalosporinase, loss of the carbapenem-specific OprD porin, and mutational overexpression of efflux pumps. In the case of horizontally acquired resistance, extended-spectrum β-lactamases and carbapenemases are of special concern. Metallo-β-lactamases are by far the most prevalent carbapenemases in P. aeruginosa [3].

Many of these mechanisms can lead to resistance to the same class of antibiotics. For instance, resistance to carbapenems can be mediated by loss of OprD porin expression, overexpression of efflux pumps, and production of metallo-β-lactamases. The combined action of these resistance mechanisms makes treating infections with P. aeruginosa especially challenging.

MULTIDRUG-RESISTANT *PSEUDOMONAS AERUGINOSA* (MDRPA): DIMENSION OF THE PROBLEM

The World Health Organization (WHO) published a priority list of antibiotic-resistant bacteria in 2017, which includes carbapenem-resistant *P. aeruginosa*. Taconelli et al. ranked the bacteria on the list based on several factors, including mortality, health burden, prevalence of resistance, resistance trend, community burden, transmissibility, preventability in healthcare and community settings, treatability, and drug develop-

ment. *P. aeruginosa* placed second on the list, following carbapenem-resistant *Acinetobacter baumannii* [4].

Moreover, *P. aeruginosa* is the sixth pathogen with the highest number of deaths attributable to bacterial antimicrobial resistance, according to 2019 data [5]. This is particularly notable since other bacteria higher on the list, such as *Escherichia coli*, *Staphylococcus aureus*, or *Klebsiella pneumoniae*, cause more infections in the community, ultimately affecting a larger number of individuals than *P. aeruginosa*.

MDRPA IN SPAIN: WHERE ARE WE?

According to the ECDC 2022 data, the rate of carbapenem-resistant *P. aeruginosa* in Spain ranges between 10% and 25% [6]. A nationwide survey conducted in 2017 with 1454 strains showed that 9% of them were multidrug-resistant, 17% were extensively drug-resistant, and 0.1% were pandrug-resistant [7]. However, it is important to bear in mind that these data are pre-pandemic and the impact of the COVID-19 pandemic on the previous distribution should be assessed. For those strains, colistin, amikacin, ceftolozane-tazobactam, and ceftazidime-avibactam showed the highest susceptibility rates. The MIC90 for the latter two was 2 and 8, respectively [7]. This reflects that the most active β-lactam against P. aeruginosa is ceftolozane-tazobactam. It is important to note that this study was conducted before the release of cefiderocol.

Among the extensively drug-resistant *P. aeruginosa* strains, 61% were found to have OprD deficiency, and 65% displayed overproduction of AmpC [7]. This reflects that the most active β-lactam against *P. aeruginosa* is Ceftolozane-tazobactam. It is important to notice that this study is before cefiderocol release.

Among the extensively drug-resistant *P. aeruginosa* strains, 61% were found to be OprD deficiency, and 65% displayed overproduction of AmpC It is worth noting the intervariability between hospitals. Clonal diversity is much lower among multidrug-resistant and especially extensively drug-resistant strains. High-risk clones have been identified, which are linked to hospital outbreaks worldwide, and all of them possess the ability to develop and transfer resistance [3]. For instance, the ST175 clone accounts for 40.9% of all extensively drug-resistant isolates in Spain [7].

Certain extensively drug-resistant clones, such as ST175, ST111, and ST235, are frequently linked to particular resistance mechanisms, which in turn are related to a resistance profile. In other words, the observed susceptibility profile should make us suspect the resistance mechanism and the clone we are dealing with because the therapeutic options will vary accordingly [3]. Therefore, MDRPA should not be uniformly treated with the same antimicrobial approach.

The IDSA guidelines recommend the use of ceftolozane-tazobactam to treat MDRPA if susceptible, when the infection is moderate to severe, or when source control is poor [8]. However, a previous multicenter study in Spain reflected that in 150 MDRPA, 68.7% were susceptible to ceftolozane-tazobactam [9]. These results support that antibiotic treatment does not end with guideline recommendations.

MORTALITY ASSOCIATED WITH MDRPA INFECTIONS

The mortality rate associated with infections caused by this bacterium is extremely high, exceeding that of S. aureus in certain types of infections, such as bloodstream infections [10]. MDRPA infections are associated with higher mortality compared to non-MDRPA infections. Inappropriate empiric treatment has been shown to increase mortality [11]. However, it should be noted that other variables might account for this outcome, such as more virulent strains or debilitated patients.

MDRPA: THERAPEUTIC OPTIONS

Quinolones are the only group of antibiotics that can be orally administered to treat P. aeruginosa infections. Aminoglycosides are used intravenously in monotherapy only for uncomplicated urinary tract infections, otherwise they are administered in combination with other antibiotics. Colistin is reserved as a last resort due to its side effects. β-lactam antibiotics are available in different levels of potency, with piperacillin-tazobactam, ceftazidime, and cefepime as the first level, followed by carbapenems in the second level, novel β-lactams-β-lactamase inhibitors in the third level, and cefiderocol in the highest level.

Avibactam is a β-lactamase inhibitor with inhibitory activity against several types of β-lactamases, including class C, class A, and certain class D enzymes. However, ceftazidime-avibactam has limitations, including vulnerability to efflux pumps and lack of activity against metallo-β-lactamases. Ceftolozane is a stable antibiotic against AmpC-type β-lactamases and efflux pumps of *P. aeruginosa*, with less potential for resistance development compared to ceftazidime. However, ceftolozane has its own limitations, including a lack of activity against metallo-β-lactamases and class A carbapenemases. [12]. During the COVID-19 pandemic, the increased use of ceftazidime-avibactam led to a rise in resistance rates to both ceftolozane-tazobactam and ceftazidime-avibactam due to a cross-resistance phenomenon induced by either antibiotic [12]. This effect should be considered when developing antibiotic rotation strategies in hospitals.

Relebactam restores imipenem activity against strains expressing AmpC overproduction and OprD deficiency, and is stable against efflux pumps and some β-lactamases (class A and D). However, it has no activity against metallo-β-lactamases and induces cross-resistance to the previously mentioned antibiotic combination.

Meropenem-vaborbactam is weaker against strains with decreased expression of OprD porins and those with efflux pumps. It also has no activity against class B β-lactamases. Its role is mainly related to KPC-producing enterobacteria rather than MDRPA [12].

Cefiderocol, as an iron chelator, enters the periplasm through active iron transporters and porins like other β-lactams, where it binds to PBPs. It has increased stability against serine- and metallo-β-lactamases and extended spectrum of activity against other non-fermentative Gram-negative bacilli. However, there is limited data on its activity against class D β-lactamases, such as *P. aeruginosa* chromosomal OXA-50. Cefiderocol has no cross-resistance with other β-lactams, although minimum inhibitory concentrations may increase [12].

MDRPA: SOME CONSIDERATIONS FOR TREATMENT CHOICE

Choosing appropriate empirical treatment for infection requires consideration of various factors, such as the clinical entity, comorbidities, and the presence of risk factors for multidrug-resistant pathogens. Local epidemiological data should be used to ensure effective treatment. [13]. Timely collection of an appropriate sample is critical for identifying the causative microorganism and facilitates appropriate antibiotic de-escalation. In addition to selecting the appropriate antibiotic, optimizing pharmacokinetics is crucial for successful treatment. [14].

Adequate control of the source of infection is key to overcoming the infection, even with optimal management of antimicrobial therapy [15].

The use of combined empirical treatment remains unclear, and the decision should be evaluated on a case-by-case basis. Although a meta-analysis showed no difference in mortality between combined antimicrobial therapy and monotherapy [16], a retrospective study reported a favorable effect of combination therapy in treating *P. aeruginosa* bacteraemia in neutropenic patients. [17]. Therefore, empirical combination therapy might be more effective than monotherapy in certain cases. The three main objectives of using more than one antibiotic are to expand the spectrum, increase the bactericidal activity during high bacterial load, and reduce the development of resistance.

The duration of treatment should not differ based on whether the infection is caused by MDRPA or a sensitive strain. If oral sequencing is possible, it should be done if the isolate is sensitive to an oral option, the patient is haemodynamically stable, there is good control of the focus, and the patient can absorb the drug to be sequenced [8].

MDRPA: THE FUTURE

Colonization by healthcare-associated pathogens often precedes infection, and the protective microbiota plays a crucial role in preventing this. Successfully decolonizing a patient or preventing colonization altogether could potentially avoid future infections. One strategy to achieve this is studying the microbiome and modifying it [18].

Furthermore, alternative treatments such as antimicrobial peptides, new antibiotics, phage therapy, nanoparticles, anti-inflammatory agents, gene editing tools, and vaccines are being developed, showing great promise for the future management of *P. aeruginosa* infections. These novel approaches offer a wide range of potential options to combat and control this pathogen [19].

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Trends in infectious diseases

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New trends in antifungal treatment: What is coming up?

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ABSTRACT

New antifungal agents are needed to overcome limitations of available ones such as poor pharmacokinetic traits, toxicity, drug-drug interactions, limited clinical efficacy, and emerging antifungal resistance. New antifungal drugs belong to well-known families (azoles, polyenes, or beta-d-glucan synthase inhibitors) or to drug families showing completely new mechanisms of action. Some drugs have a head start in terms of potential to reach the clinical setting and are here reviewed.

Keywords: Fosmanogepix, olorofim, ibrexafungerp, rezafungin

BACKGROUND

Understanding of invasive fungal infections requires taking into account multidirectional interactions among patients, causative agents, and antifungal drugs (Figure 1). New antifungal agents are needed to overcome limitations of available antifungals such as poor pharmacokinetic traits, toxicity, drug-drug interactions, limited clinical efficacy, and emerging antifungal resistance. Mapping out new drugs lies on expanding the number of the ones belonging to well-known families (azoles, polyenes, or beta-d-glucan inhibitors) or designing molecules showing completely new mechanisms of action. Some drugs have a head start in terms of potential to reach the clinical setting and are here reviewed (Figure 2); their main pharmacokinetic properties and potential clinical niches are summarised in Tables 1 and 2.

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NEW AZOLES

Opelconazole [1,2]. It is a new synthetic azole designed for topical use and nebulised administration; the drug shows high exposure and long retention at the site of infection (lungs). Since it is not absorbed, systemic effects such as toxicity and liver drug-drug interactions are avoided. It is an inhibitor of *Aspergillus* sterol 14-alpha-demethylase (CYP51 enzymes), similarly to posaconazole. Its spectrum of activity has not been well studied yet but it shows *in vitro* activity against *C. auris*, *C. albicans*, *C. glabrata*, *C. krusei*, *Cryptococcus*, *A. terreus*, and *A. fumigatus* (synergistic activity combined with voriconazole or posaconazole has been observed against the latter). *In vitro* activity against *A. flavus*, *A. niger*, and Mucorales is poor. It shows dose-dependent activity, and the best PK/PD index predictor is unknown. Data from animal models showed efficacy of opelconazole for the treatment and prevention of invasive pulmonary aspergillosis. Clinical data from humans is still very limited.

Oteseconazole [3,4]. It is a synthetic tetra-azole showing a high affinity to the fungal Cyp51 that confers the drug an enhanced specificity for fungal Cyp51 and fewer drug-drug interactions and good tolerability. It has shown *in vitro* activity against *Candida* and the potential activity against moulds is unknown. It has been under clinical evaluation for the treatment of superficial *Candida* infections including vaginitis and onychomycosis; it was approved by the FDA in 2022 for the treatment of vulvovaginal candidiasis.

POLYENES

Encochleated amphotericin B [5,6]. Amphotericin B was marketed in the 50's and shows the broadest fungicidal spectrum of *in vitro* activity. Its use is hampered by toxicity

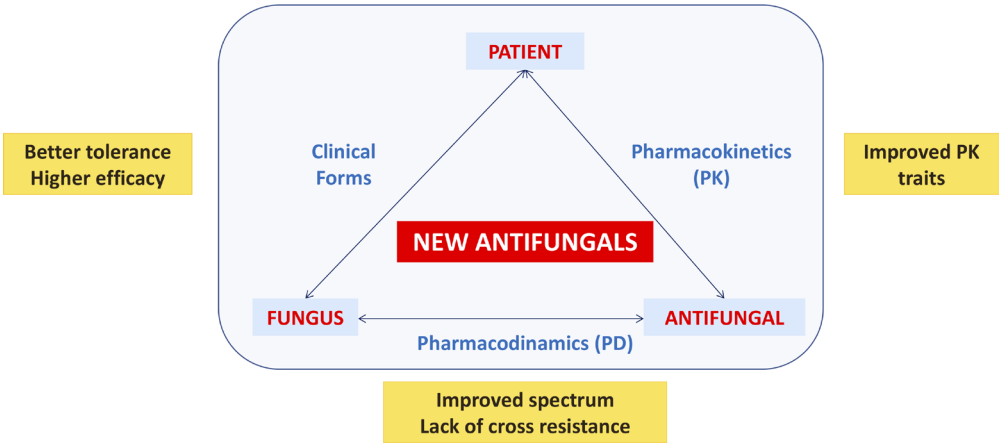

Figure 1 Graph showing interactions among the three elements playing a role in invasive fungal infections (patients, aetiological agents, and antifungal drugs)

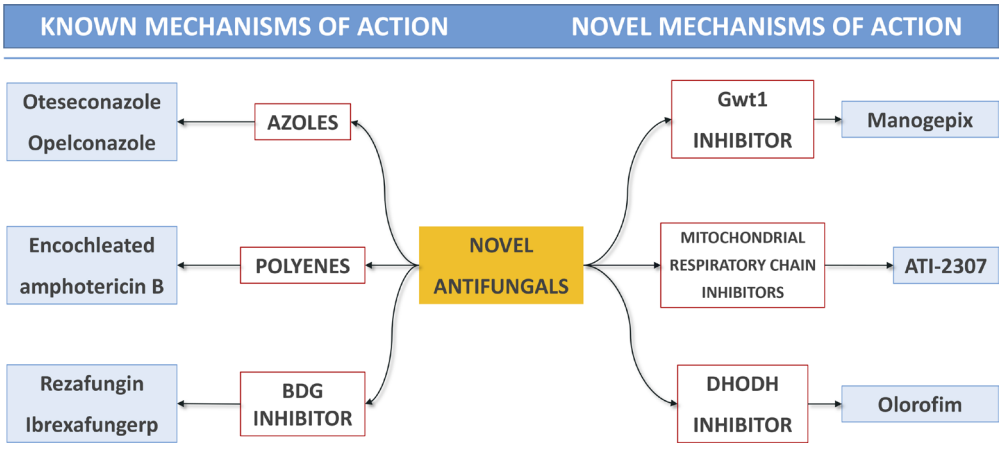

Figure 2 New antifungal agents in the horizon for the treatment of fungal infections

and formulation problems (highly water-insoluble and self-aggregate tendency). Vehicles in the formulation are needed and current formulations allow intravenous administration exclusively. The molecule gets protection into encochleating lipid-based vehicles, which means increasing chemical stability, safety and clinical efficacy, and allowing oral absorption. Encochleated amphotericin B is more stable than liposomes and less prone to oxidation, resists enzyme degradation, and shows slow release of the drug. The spectrum of activity is similar to other formulations of the drug (with limited activity against *A. terreus*, *A. flavus*, and *A. nidulans*) and shows dose-dependent activity; the best PK/PD index predictor is unknown. Data from animal models showed efficacy of encochleated amphotericin B for the treatment systemic candidiasis, cryptococcal meningitis, and invasive pulmonary aspergillosis. Clinical data from humans is still very limited.

NEW BETA-D-GLUCAN INHIBITORS

Rezafungin [7,8]. It is a second generation echinocandin whose mechanism of action and spectrum of activity is similar to the currently available echinocandins, including *C. auris*. It is a derivative of anidulafungin in which the modification cyclic core conferred the drug a safer profile and long half-life (130 hours) which in turn resulted in high drug exposure, one-week single dose administration, and lower induction of FKS mutations. It shows concentration-dependent activity (*in vitro*) or dose-dependent activity (animal models); the best PK/PD index predictor is AUC / MIC (*Candida*), or AUC / MEC or C_{max} / MEC (*Aspergillus*). Rezafungin showed non-inferiority compared to caspofungin for the treatment of patients with candidaemia and FDA approved the drug for the treatment of candidaemia (it is under evaluation by EMA now). Clinical trials

Table 1 Main pharmacokinetic properties of the new antifungal agents

Drug	Administration			Penetration				Expected drug-drug interactions	Excretion
	Oral	IV	Other	CNS	Eye	Urine	Tissue distribution		
Opelconazole	Unavailable	Unavailable	Available (Nebulised)	No	No	No	Topical use (lungs)	Non expected	Unknown
Oteseconazole	Available	Unavailable	Unavailable	No	No	Yes	Unknown	Non expected	Faeces and urine
Enclocheated amphotericin B	Available	Unavailable	Unavailable	Yes	Yes	Yes	Wide	Non expected	Unknown
Rezafungin	Unavailable	Available	Unavailable	No	No	No	Wide	Non expected	Biliary elimination
Ibrexafungerp	Available	Available	Unavailable	No	No	Yes (uvea)	Wide	Moderate	Biliary elimination
Manogepix	Available	Available	Unavailable	Yes	Unknown	Unknown	Wide	Moderate	Unknown
Olorofim	Available	Available	Unavailable	Yes	Unknown	Unknown	Wide	Moderate	Unknown

IV, intravenous; CNS, central nervous system

assessing the role of rezafungin for the prevention of invasive fungal infections in allogenic SCT, and evaluating pharmacokinetic properties in paediatric patients, are underway.

Ibrexafungerp [8,9]. It is a semi-synthetic derivative of enfumafungin, a tri-terpenoid non-competitive inhibitor of 1,3-B-D-glucan synthase enzyme complex. It is not an echinocandin from a chemical point of view, but its mechanism of action is similar to the one of the echinocandins, yet the exact point of drug binding to the enzyme might not be identical. It retains some activity against echinocandin-resistant *Candida* isolates, can be orally administered, and has shown high penetration into intra-abdominal lesions. It shows concentration-dependent activity (*in vitro*) or dose-dependent activity (animal models); the best PK/PD index predictor is AUC / MIC (*Candida*), or AUC / MEC or C_{max} / MEC (*Aspergillus*). Ibrexafungerp has shown encouraging results on treatment of non-neutropenic patients with invasive candidiasis, women with vulvovaginitis (current approved indication), and is under evaluation for the treatment of patients with IFI refractory to other treatments, patients with *C. auris* infections, or patients with invasive aspergillosis (treatment combined with voriconazole).

ACYLTRANSFERASE ENZYME (GWT1) INHIBITORS

Fosmanogepix [10,11]. It is a prodrug (manogepix is the active moiety) that inhibits the fungal acyltransferase enzyme (Gwt1), an important component of the glycosylphosphatidylinositol (GPI)-anchored protein maturation pathway, that is essential for trafficking mannoproteins to the fungal cell membrane and wall. Given its new mechanism of action, it shows a broad spectrum of antifungal activity against *Candida* spp. (except for *C. krusei*), *Cryptococcus* and other non-Candida yeasts, *Aspergillus* spp and *Fusarium* spp, and lacks of cross-resistance. The best PK/PD indexes predictor of response are AUC/MIC and AUC/MEC (aspergillosis), and AUC/MIC (invasive candidiasis). The drug is under clinical evaluation for the treatment of candidiasis (including *C. auris*), aspergillosis, and other mould infections (*Scedosporium* and *Fusarium*). Preliminary data (including tolerability and clinical efficacy) are encouraging.

MITOCHONDRIAL RESPIRATORY CHAIN INHIBITORS

ATI-2307 [12]. It is an aromatic diamidine pentamidine-like compound with antifungal activity against *Candida* spp, *Aspergillus* spp., *Fusarium*, and *C. neoformans*. ATI-2307 acts by means of selectively inhibition of yeast mitochondrial respiratory chain complexes III and IV. Animal models data have shown efficacy of the compound in the treatment of cryptococcal meningitis in rabbits.

DIHYDROOROTATE DEHYDROGENASE INHIBITORS

Olorofim [13,14]. It is a first-in-class drug belonging to a new family of antifungal agents, the orotomides, whose mechanism of action lies on the inhibition of the pyrimidine biosynthesis by blocking the action of the enzyme dihydroorotate dehydrogenase (DHODH). Olorofim shows a peculiar spectrum of activity and lacks *in vitro* activity against *Candida* spp and Mucorales. In contrast, it has potent activity against most of clinically relevant *Aspergillus* spp. (including azole-resistant strains) and *Scedosporium*. The ratio of the minimum total plasma concentration / MIC (C_{min}/MIC) was the PK/PD index that best predicts clinical response. Currently, olorofim is under evaluation for the treatment of invasive mould infections in patients with limited treatment options.

Table 2 Potential clinical niches for new antifungal agents

	Preclinical name	Company	Prophylaxis	Vaginitis	Candidaemia	Aspergillosis	Cryptococcosis	Other IFIs
Opelconazole	PC945	Pulmocide Ltd	++ (Lung transplant, cystic fibrosis)	+	+	++	-	-
Oteseconazole	VT-1161	Mycovia	+	++	+	+	+	+
Enclocheated amphotericin B	MAT-2203	Matinas Biopharma	-	-	+	+	++	-
Rezafungin	CD101 SP-3025 Biafungin	Cidara→ Mundipharma	++	-	++	+	-	+
Ibrexafungerp	SCY-078	Scynexis→ GSK	++	++	++	++	-	+
Manogepix	APX001A	Amplyx→ Pfizer→ Basilea	+	+	++	++	+	++
Olorofim	F901318	F2G	-	-	-	++	-	++

- no clinical trials and unlikely for the indication based on in vitro spectrum of activity and PK properties, or discouraging clinical data
+ no clinical trials but room for indication based on in vitro spectrum of activity and PK properties
++ clinical trials and likely for the indication based on in vitro spectrum of activity, PK properties, and clinical data

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JG holds a permanent position at the *Fundación para Investigación Sanitaria del Hospital Gregorio Marañón*.

TRANSPARENCY DECLARATIONS

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Trends in infectious diseases

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What are the most relevant publications in Clinical Microbiology in the last two years?

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ABSTRACT

This minireview describes some of the articles published in the last two years related to innovative technologies including CRISPR-Cas, surface-enhanced Raman spectroscopy, microfluidics, flow cytometry, Fourier transform infrared spectroscopy, and artificial intelligence and their application to microbiological diagnosis, molecular typing and antimicrobial susceptibility testing. In addition, some articles related to resistance to new antimicrobials (ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol) are also described.

Key words: innovative diagnostic technologies, microbiological diagnosis, antimicrobial susceptibility testing, resistance to new antimicrobials

INTRODUCTION

Over the last years, the development of new technologies has also reached clinical microbiology laboratories and transformed the care of infectious diseases. The use of multiplex syndromic panels and point of care testing for infectious diseases, molecular diagnostics for fungal infections, rapid genotypic and phenotypic antimicrobial susceptibility testing, introduction of next-generation sequencing into clinical diagnostics and laboratory diagnostic stewardship have improved patient care. In addition, the diagnostic potential of innovative molecular technologies and harnessing big data through artificial intelligence in clinical microbiology offer a great opportunity to move forward.

On the other hand, antimicrobial resistance has even reached the most recently introduced new antimicrobials and is a cause for concern that needs to be rapidly detected to prevent its spread.

This minireview describes some of the articles published in the last two years related to innovative technologies and resistance to new antimicrobials.

NEW TECHNOLOGIES APPLIED TO MICROBIOLOGICAL DIAGNOSTICS

The manuscript of Zhao L, et al [1] is an excellent review describing the usefulness of the CRISPR-Cas13a system as a tool for molecular diagnostics, gene therapy, gene editing, and RNA imaging. The clustered regularly interspaced short palindromic repeats (CRISPR) system is a natural adaptive immune system of prokaryotes. Additional elements of the CRISPR system include the leader sequence and CRISPR-associated (Cas) genes. Cas13a possesses two RNase activities, one for pre-crRNA processing and the other for cis-cleavage of the target RNA and trans-cleavage of non-specific RNAs. Cas13a processes pre-crRNA into mature crRNA independently and combines with its crRNA to form the surveillance complex that recognizes the foreign target RNA and cleaves the target and surrounding ARNs. Subsequently, products trans-cleaved by Cas13a system are recognized with fluorescence or lateral flow readouts. Because of this trans-cleavage activity and the high specificity of its CRISPR RNA, the CRISPR/Cas13a system has been the most widely characterized for its application in molecular diagnostics including the detection of pathogens like viruses, bacteria, parasites, and fungi. The CRISPR-Cas13a system can improve sensitivity, specificity, operability, portability and cost of other diagnostic methods such as antigen detection, PCR or ADN sequencing. One example of application of the CRISPR-Cas13a system is the study of Fozouni P, et al [2] for the detection and quantification of SARS-CoV-2 directly from nasopharyngeal samples without pre-amplification. The viral load was directly quantified using enzyme kinetics and the assay is integrated with a reader

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device based on a mobile phone that allows for portable and sensitive readout. The sensitivity was ~100 copies/µL in under 30 min of measurement and accurately detected pre-extracted RNA from a set of positive clinical samples in under 5 min. This low-cost assay has the potential to be used as point-of-care screening for SARS-CoV-2.

Another innovative technology is the surface-enhanced Raman scattering (SERS). This is a spectroscopic technique based on vibrational analysis and fluorescence detection. Its advantages include fluorescence quenching, short time of measurement, high quality spectra, and low costs of analysis, being an appropriate method for biomedical applications and has been applied for the diagnosis of various infectious diseases [3]. By using this technique, the study of Berus SM, et al. [4] detected the presence of *Neisseria gonorrhoeae, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum*, and *Haemophilus ducreyi* directly in men's urethra swabs in less than 15 min. The SERS spectra were analyzed by applying PCA (principal component analysis) partial least square discriminant analysis (PLS-DA), and soft independent modelling of class analogies (SIMCA) and identified the individual species of the *Neisseria* genus with high accuracy. The prediction accuracy reached 89% for SIMCA and 100% for PLS-DA. The authors indicate that the simplicity, high sensitivity, reproducibility, and specificity, open a new path in the improvement of the point-of-care applications.

Microfluidic chip technology is a system in which very small amounts of fluid are used. The fluid behaviour at the microscale (microchannels: 10-500 nm) differs from the macroscale since surface tension and energy dissipation are different, the flow is laminar, without turbulence, only diffusion is involved in fluid mixing, and there is a very high surface-to-volume ratio which accelerates chemical reactions. This technology can also be used to integrate the process units required for nucleic acid detection such as sample pretreatment, nucleic acid extraction, target sequence amplification, and signal detection, into one single micron-scale chip (lab-on-a-chip). The manuscript of Gao D, et al [5] reviews the research progress on microfluidic chip-based recombinase polymerase isothermal amplification technology. The advantages of this technology include high integration, compactness, portability and less sample consumption. In the same line, the research study of Ma L, et al. [6] presents a novel example of developing a polymer-based microfluidic device for the identification and antimicrobial susceptibility testing (AST) of *Campylobacter* spp. The assay uses chromogenic agar as selective cultivation medium and employes advanced design of air vents and zigzag channels to prevent the cross-contamination of antibiotics in different testing chambers, ensuring accurate AST results. The chromogenic medium and antibiotics were loaded in the device, and the growth of *Campylobacter* spp. was visualized by color change due to chromogenic reactions. The platform achieved 100% specificity for *Campylobacter* spp. identification. *C. jejuni, C. coli,* and *C. lari* were detected in artificially contaminated milk and poultry meat, with detection limits down to $1x10^2$ CFU/ml and $1x10^4$ CFU/25 g, respectively. The MICs and susceptibility profiles of *Campylobacter* isolates were also tested by on-chip AST, showing high coincidences in the MIC (91% to 100%) with the conventional agar dilution method against ampicillin, tetracycline and ciprofloxacin. For a presumptive colony, on-chip identification and AST were completed in parallel within 24 h., representing a rapid, portable, and cost-effective approach to detect antibiotic-resistant *Campylobacte*r spp.

Flow cytometry is an analytical method that allows the rapid measurement of light scattered and fluorescence emission produced by suitably illuminated cells. The cells, or particles, are suspended in liquid and produce signals when they pass individually through a beam of light. This technology has been widely used in basic microbiology for the simple and rapid assessment of the viability of a microorganism. In the study of Silva-Dias A, et al [7] the authors evaluate the FASTinov® flow cytometry kit on positive blood cultures for the rapid determination of AST with a time to result of less than 2 h. Two kits were evaluated, one for Gram-negative and other for Gram-positive microorganisms in spiked blood cultures with well-characterized bacteria, and also using positive blood cultures from patients. Results were compared with the standard disk diffusion method, that was used as the reference. After 1 h of incubation at 37°C, bacteria were analyzed using a cytometer. Categorical agreement values for the Gram-negative panel were 96.8% based on EUCAST criteria and 96.4% based on CLSI criteria. The percentages of very major errors (VME) were 0.6% and 0.4% when using EUCAST and CLSI criteria, respectively, and were mainly observed with amoxicillin-clavulanate, cefotaxime, ceftazidime, and gentamicin. The kit also provided information regarding the presence of extended-spectrum beta-lactamases and carbapenemases. For the Gram-positive panel, categorical agreement was 98.6% when using both criteria, and showed 0.4% of VME (gentamicin and *Staphylococcus*) when using EUCAST and no VME when CLSI criteria was used. This study represents the utility of flow cytometry as a rapid alternative for direct antimicrobial susceptibility testing from positive blood cultures.

Fourier transform infrared spectroscopy (FTIR) is a mass spectrometry technology that analyses the absorption in the infrared spectrum of specific bonds present in different groups of molecules (lipids, proteins, carbohydrates and nucleic acids). This automated system has been used for real-time molecular typing for outbreak monitoring. The study of Passaris I, et al [8] presents the validation of FTIR for the capsular typing of *Streptococcus pneumoniae,* and conclude that this is a rapid and cost-effective technique and medium-throughput alternative to the classical phenotypic techniques. The IR Biotyper was first trained with a set of 233 strains comprising 34 different serotypes and the acquired spectra were used to create a dendrogram where strains clustered together according to their serotypes and to train an artificial neural network (ANN) model to predict unknown pneumococcal serotypes. Using 153 additional strains, the accuracy for determining serotypes represented in the training set was

98.0%, and using 124 strains representing 59 non-training set serotypes, the accuracy was 71.1% for the categorization as being non-training set serotypes. Although the method needs to be improved, it is a potential future alternative to conventional methods.

Artificial intelligence (AI) is a technology that for some years now has been present in our daily lives, including microbiological diagnostics. AI is a combination of algorithms to create machines that mimic human intelligence to perform tasks and can improve as they gather new information. AI is applicable to the diagnosis of infectious diseases including the detection of patients at risk of sepsis, the early detection of infections, the diagnosis of viral respiratory infections, and also as an aid in the radiological diagnosis of pulmonary tuberculosis [9]. One application of AI in clinical microbiology is the reading and interpretation of antibiograms using the disk diffusion method as described in the study of Pascucci M, et al. [10]. The system consists of an offline smartphone application for antibiogram analysis that captures antibiogram images with the phone's camera, and the user is guided throughout the analysis on the same device by a user-friendly graphical interface. An embedded expert system validates the coherence of the antibiogram data and provides interpreted results. In the study, the authors validate this fully automatic measurement procedure and obtained an overall agreement of 90% on susceptibility categorization against a hospital-standard automatic system and 98% against manual measurement (gold standard), with reduced inter-operator variability. The automatic reading of AST is entirely feasible on a smartphone. The authors conclude that this application is suited for resource-limited settings, and has the potential to significantly increase patients' access to AST worldwide.

RESISTANCE TO NEW ANTIMICROBIALS

Carbapenemase-producing Enterobacterales, mainly *Klebsiella pneumoniae*, have emerged and spread world-wide as a major cause of infections associated with high morbidity and mortality. In recent years, novel beta-lactam-beta-lactamase inhibitor combinations, such as ceftazidime/avibactam (CZA), meropenem/vaborbactam (MVB), and imipenem/relebactam (IMR), have been introduced in clinical practice, and are useful to treat infections caused by KPC-producing *K. pneumoniae* (KPC-Kp). However, acquired resistance to these combinations has been reported in KPC-Kp. Di Pilato V, et al [11] described an outbreak caused by CZA-resistant KPC-Kp, which was also variably resistant to MVB and IMR. Whole-genome sequencing revealed that the outbreak was multi-clonal and resistance to CZA was primarily mediated by overproduction of KPC-3 associated with increased gene dosage, a mechanism accounting for cross-resistance to MVB in most cases, and to IMR in a single KPC-Kp isolate; multiple alterations of the OmpK36 porin were also detected and mutated KPC (KPC-53) was detected in a single case. All cases were associated with previous CZA exposure. Nicola F, et al [12] described a clonal outbreak caused by 6 isolates of KPC-Kp sequence type 11 producing KPC variants resistant to CZA: KPC-31 variant in 5 cases and a novel variant, named KPC-115, in one case. Three patients had previously received CZA. These two studies reflect the need to monitor the evolution of the resistance, possibly coupled with a genomic analysis in order to understand the mechanisms of resistance to these antimicrobial combinations.

Regarding metallo-beta-lactamases (MBLs), these belonging to the NDM group are the most frequently identified acquired carbapenemases worldwide. MBLs hydrolyze all beta-lactams except monobactams, and they are not inactivated by currently commercialized beta-lactamase inhibitors. Nevertheless, very recent therapeutic options are promising, such as cefiderocol (FDC) and aztreonam/avibactam (ATM-AVI). The study by Poirel L, et al [13] described a ST167 *Escherichia coli* clinical isolate that produced NDM-35 and was resistant to carbapenems, ATM-AVI, and FDC, showing a 10-fold increased hydrolytic activity against cefiderocol compared to NDM-1. The isolate also produced a CMY-type beta-lactamase, exhibited a four amino-acid insertion in PBP3, and possessed a truncated iron transporter CirA protein (resistance to FDC), leading to resistance to virtually all beta-lactams. Finally, the study of Lan P, et al [14] from China, presents 2 strains of *K. pneumoniae* isolated from bloodstream infections that were resistant to FDC. One isolate carried the beta-lactamases SHV-12, DHA-1 and NDM-1, and the other carried the MBL NDM-5 and also presented a deficiency in the CirA protein, leading to high-level cefiderocol resistance (MIC >256 mg/L). It is noteworthy that these strains were isolated prior to the approval of cefiderocol clinical use in China.

CONFLICT OF INTEREST

Author declares no conflict of interest.

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Trends in infectious diseases

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The Magnificent Seven: Seven good publications in infectious diseases

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ABSTRACT

The world of infectious diseases, for various reasons, before and after the COVID-19 pandemic, capture the attention of the scientific community, either due to the epidemiological data of various microbial agents that are emerging, due to the implementation with successful results of new diagnostic strategies or due to the appearance of new therapeutic options, which encourage healthcare workers to continue on the front line.

Topics such as antimicrobial resistance, *S. aureus* bacteremia, clostridioides difficile, short treatments for tuberculosis, prosthetic joint infection or invasive fungal infections are included.

In this article, we want to highlight, among many others, seven recently published articles that deserve our attention, full of useful information to keep us updated.

Keywords: antimicrobial resistance, catheter-related bacteremia, anti-tuberculosis drugs

The broad scientific production between 2020 and 2022 has left us with a huge number of interesting scientific articles. Excluding HIV and COVID-19 we want to highlight, in an attempt to cover different topics, seven of the most impressive scientific publications.

The first article selected [1], studies the impact of antimicrobial resistance (AMR) in 204 countries. It is also reviewed the deaths and disability attributable to and associated with 23 multidrug-resistant bacteria and 88 pathogen-drug combinations. The greatest number of deaths was attributed to methicillin-*resistant Staphylococcus aureus* (MRSA), while other bacteria with multidrug-resistant spectrum such as *Escherichia coli*, *Acinetobacter baumannii* or *Klebsiella pneumoniae* were relegated to the background. In 2019, there were 4.95 million deaths associated with antimicrobial resistance, including 1.27 million deaths that were directly attributable to bacterial AMR. The region with the highest attributable mortality in the world was Sub-Saharan Africa.

This study reveals the different epidemiology of AMR bacteria depending on the country's income. *E. coli* and *S. aureus* were more frequent in countries with high incomes, whereas *K. pneumoniae* and *S. pneumoniae* acquire more importance in those with lower incomes. The respiratory tract infections were the main source of infection in those countries with lower incomes.

Talking about Clostridioides difficile, we have selected the Katzman M. et al [2] article which highlights the introduction of two different interventions to reduce the incidence of *C. difficile* infections (CDI) in an university hospital, wherein despite of the cleaning and contact protocols, the incidence of CDI increases up to approximately 160 cases per year, in the last three years.

The first intervention was carried out during admission, consulting if the patient had one or more liquid stools in the last 24 hours. If the answer was affirmative, contact measures were established and CD PCR was requested. The next step consisted in the toxigenic antigen detection by enzyme immunoassay (EIA) in samples with positive result by polymerase chain reaction (PCR). If the EIA was negative, the patient did not require treatment but contact isolation, and if the toxigenic gene was detected, an internal hospital protocol was launched. Treatment with fidaxomicin was included on it.

Other minor measures were also carried out which included proton-pump inhibitors drugs reduction, usage of probiotics for some patients on antibiotics, and prophylaxis with oral vancomycin for patients receiving antibiotics who had CDI in the previous year. The results obtained one year after the implementation of these interventions confirmed a significant and

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maintained reduction in the cases of CDI over time (from 161 to 63 cases). Only 45% of patients were PCR (+)/EIA (+), and they had similar outcomes to the PCR (+)/EIA (-) patients.

Central Line-Associated Bloodstream Infections (CLABSIs) continues to be an important source of nosocomial infection. For this reason, we chose an update of the 2014 guidelines from *Strategies to Prevent Central Line-Associated Bloodstream Infections in Acute-Care Hospital* [3]. Some of the recommendations to prevent CLABSI at insertion were the usage of the subclavian site to reduce infectious complications when the catheter is placed in the Intensive Care Units (ICU) setting, guidance by ultrasound for catheter insertion and usage of an alcoholic chlorhexidine antiseptic for skin preparation. After insertion, it is recommended the routine replacement at intervals up to 7 days of administration sets not used for blood, blood products or lipid formulations. Approaches that should not be considered as a routine part of CLABSI preventions are the use of antimicrobial prophylaxis for short-term or tunnelled catheter insertion or while catheters are *in situ* and not to do routinely replace of the Central Venous Catheters (CVC) or arterial catheters.

Injection drugs use is an important risk factor for the development of infective endocarditis (IE), however, advances in diagnosis and treatment have been slow. The American Heart Association along with a panel of experts have developed a scientific support document for clinicians managing IE in people who inject drugs (PWID) [4]. This document has three major sections of clinical expertise that include the integration of addiction consultation, antimicrobial therapy and cardiac valve surgery management.

The antimicrobial therapy management is focused on the treatment of *S. aureus,* as it is the most frequent attributable to injection drug use (85%). The standard of care of IE attributable to *S. aureus* has included 6 weeks of intravenous (IV) antibiotics, however the group of Baddour LM et al recognizes that 6 weeks of intravenous antibiotics is often not feasible for all PWID. Partial intravenous therapy followed by oral antibiotic treatment to complete a total of 6 weeks is growing evidence and it can be an option for patients who cannot complete 6 weeks of its treatment. For this regimen, best practice would offer oral antibiotics or long-acting lipoglycopeptides dalbavancin or oritavancin. Surgery should be postponed until the end of antibiotic treatment, except in serious cases such as heart block, persistent bacteremia, or the presence of intracardiac abscesses.

The treatment of joint prosthesis-associated infections deserves a special article in the New England Journal of Medicine [5]. This is an open-label, randomized, and controlled, non-inferiority trial to compare 6 weeks with 12 weeks antibiotic therapy in patients with confirmed prosthetic joint infection. The study enrolled 410 patients from 14 French hospitals. This trial revealed results in favor of the 12-week treatment (9.4% of persistent infections) compared to the 6-week treatment (18.1%). Results after debridement or replacement in two stages, for hip or knee prostheses, in the first episode or recurrent episode, the prognosis was more favorable in patients who completed 12 weeks of treatment, independently of these variables.

Adherence to tuberculosis treatment is a worrying issue worldwide, especially in underdeveloped countries. Our sixth article [6] is an opel-label, phase 2-3, multicenter, randomized, controlled, non-inferiority trial conducted by the Tuberculosis Alliance together with Médecins Sans Frontières. The aim of the study was to evaluate the efficacy and safety of 24-week oral treatment regimen for rifampicin-resistant TB. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen. The study enrolled 301 patients who were 15 years of age or older and had rifampicin-resistant pulmonary tuberculosis. The primary outcome was an unfavourable status at 72 weeks after the randomization and the secondary outcome was to study the safety profile of treatment with BPaLM regimen. The study demonstrated that 24-week BPaLM regimen was non-inferior to conventional treatment with better safety profile.

Finally, we highlight the magnificent review on invasive fungal infections in COVID patients published in Nature in August 2022 [7]. This review addresses the epidemiology, risk factors, predisposing characteristics of the host, and immunological mechanisms involved in the pathogenesis of fungal co-infections by COVID-19.

The main groups of fungal pathogens cause co-infections in COVID-19 are *Aspergillus*, *Mucorales* and *Candida*, including *Candida auris*. It is to be noted the wide heterogeneity of the clinical manifestations or incidence between different geographical regions, as it occurs with COVID-19 associated mucormycosis (CAM). Rhino-orbital-cerebral disease is more frequent in Asian countries while in our media the pulmonary disease is prevalent. The diagnosis of these entities continues to be a challenge. The current tools available for diagnosis such as galactomannan, β-1,3-glucan or PCR in bronchoalveolar lavage samples offer us complex results to interpret in the clinical context of each patient. The culture of non-invasive respiratory samples has a low sensitivity and other associated pathogens are isolated in 50% of cases. The difficulties due to the low diagnostic yield of probability or possibility of invasive fungal infections of conventional cultures together with the low positive predictive value of the new techniques make it necessary to reach an equilibrium between classical techniques and biomarkers based on the patient's risk factors and their clinical and radiological data.

CONFLICT OF INTEREST

Author declares no conflict of interest.

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Evaluation questionnaire

XIII Updating Course of Antimicrobials and Infectious Diseases 2023

1. The results of a clinical trial evaluating the usefulness of Ceftobiprole in the treatment of patients with complicated *S. aureus* bacteremia have been presented at ID Week. Say if you remember the comparator drug:

a) Vancomycin
b) Daptomycin
c) Dalbavancin
d) Any of the above would apply

2. All of the following drugs have been discussed in the list of agents potentially available in the near future, in antifungal therapy, with one exception to note:

a) Tufafungerp
b) Ibrexafungerp
c) Olorofim
d) Otesaconazole

3. The risk of transmission to their partners through sexual intercourse of HIV infection in persons with undetectable viral load (<200 copies/mL) is:

a) There is a risk of transmission so you should always use barrier methods.
b) It depends on the patient's CD4 lymphocytes, if they are low the risk is significant.
c) Undetectable is untransmissible, it is not necessary to use barrier methods.
d) The risk of transmission in anal intercourse is significant.

4. Survival of people living with HIV (PLWHIV) is:

a) It is lower than seronegative persons with the same characteristics by about ten years.
b) PLWHIV with viral suppression have a survival similar to the general population.
c) PLWHIV with low CD4s have similar survival
d) The risk of mortality in PLWHIV is related to the increase in cardiovascular disease in these patients.

5. Point out the incorrect one about aging in people living with HIV (PLWHIV)

a) Antiretroviral treatment slows aging
b) PLWHIV have accelerated aging data
c) Accelerated aging is seen in people with poorer HIV control
d) Telomere length and DNA methylation are affected in PLWHIV.

6. Regarding *Streptococcus* spp. bacteremia, which of the following is true?

a) The different species of *Streptococcus viridans* have the same risk of endocarditis.
b) Different species of *Streptococcus* spp. have the same risk of colorectal cancer
c) They do not always have clinical significance
d) All are false

7. In relation to infective endocarditis due to the following bacteria, which has been associated to a lesser degree with the existence of colorectal cancer?

a) Staphylococcus aureus
b) Streptococcus gallolyticus
c) Enterococcus faecalis
d) Clostridium septicum

8. Which of the following antibiotics is a treatment of choice for any of the frequent etiologies of infective endocarditis according to the European and American Guidelines?

a) Dalbavancin
b) Ceftriaxone
c) Ceftaroline
d) Oritavancin

9. Mark the correct one of the following statements:

a) The terms bacteremia and sepsis can be used interchangeably.
b) Sepsis is a complex disease, induced by infection, in which an altered host response and involvement of the main vital organs converge.
c) The diagnosis of sepsis is microbiological.
d) Answers b and c are correct

10. The creation of a specific code for sepsis is due to the fact that:

a) It is the leading infectious cause of death
b) The associated mortality can be combated with a correct diagnosis and appropriate management in the first hours of life
c) Kumar established more than 10 years ago that mortality increases by approximately 7.6% for every hour of delay in adopting appropriate measures.
d) All of the above are true

11. Regarding the establishment of a microbiological sepsis code:

a) The measures to be adopted should be the same in all laboratories.
b) Only the blood cultures of these patients should be prioritized.
c) When choosing the actions to be taken in the laboratory, the impact they will have on the patient should be taken into account.
d) It should not affect the time to issue results

12. Point out the wrong answer about Nosocomial Pneumonia

a) The mortality rate for NN ranges from 20-50% and can reach 75% in some specific settings or when caused by multidrug-resistant (MDR) pathogens.
b) It represents the most frequent nosocomial infection in the critical care setting.
c) Intubated or not, the median onset of NN is around 7-10 days after admission.
d) All are correct

13. Indicate which of the following sensitivity percentages is incorrect (results obtained 2021-2022)

a) 20-40% of healthcare-associated Enterobacteriaceae isolates are resistant to 3rd generation cephalosporins (BLEE or AmpC).
b) 2-16% of healthcare-associated Enterobacteriaceae isolates are resistant to carbapenemics
c) The resistance rate in clinical isolates of Pseudomonas aeruginosa to classical antibiotics in nosocomial pneumonia (meropenem, piperacillin-tazobactam) in critical care units is around 30%.
d) All the percentages shown are correct.

14. Mark the incorrect answer among the new antimicrobials with potential use in NN (ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, meropenem-vaborbactam, imipenem-relebactam).

a) Diffusion to the pulmonary ELF exceeds 60% of the plasma concentration in all of them, which can be increased by extending the infusion time (in those time-dependent).
b) The proximity between MIC (Minimum Inhibitory Concentration) and MBC (Minimum Bactericidal Concentration) is able to condition both the activity of the antibiotic at a known concentration and the intra-treatment resistance.
c) There is evidence that ceftolozane-tazobactam is able to decrease mortality with respect to the comparator in the subpopulation of patients with NN and bacterial isolation in culture (HBAP).
d) Answers 2 and 3 are correct

15. Point out the incorrect answer regarding immunization and the risk of progression of COVID-19 among the transplanted population

a) Unimmunized OST patients have a 20.5% to 27% risk of mortality. In addition, infection is associated with greater deterioration of renal function at 90-d
b) TOS patients have a lower vaccine response than non-transplanted patients, reaching, at best, 60-80% within 4 months of the third dose.
c) Mortality among vaccinated OST recipients with infection remains around 10%.
d) All the answers are correct

16. In a mild SARS-CoV-2 infection (day 2 from the onset of symptoms), in a transplant patient, with GFR < 20ml/h, the antiviral treatment indicated is the following:

a) No treatment is required as it is a mild infection.
b) Molnupiravir
c) Remdesivir
d) Nirmatrelvir/ritonavir

17. In a renal transplant patient on tacrolimus treatment with mild SARS-VoV-2 infection (4 days from symptom onset), treatment could include all but:

a) Molnupiravir
b) Remdesivir
c) Nirmatrelvir/ritonavir
d) Sotrovimab

18. Select the best therapeutic strategy to prescribe for a transplant patient with persistent viral replication and interspersed symptomatic periods since 2 months:

a) No treatment required
b) Monotherapy with molnupiravir for 5 days
c) Monotherapy with remdesivir for 5 days
d) Combination therapy with two antivirals for extended duration

19. Which of the following antivirals has no activity against SARS-CoV-2?

a) Nirmatrelvir
b) Favipiravir
c) Ritonavir
d) Molnupiravir

20. It is recommended that molnupiravir be initiated within the first ... days of symptom onset.

a) 5
b) 7
c) 10
d) 14

21. A 67-year-old male patient, liver transplanted in 2014 for hepatocarcinoma, on immunosuppressive treatment with mycophenolate mofetil, chronic renal insufficiency (clearance of 49) by tacrolimus, and vaccinated with three doses against SARS-CoV-2 (last November 2021) who came to the emergency department in December 2022 for febrile and cough of 36 hours of evolution. Physical examination with no crackles. O2 saturation of 97%, room air. Chest X-ray without infiltrates. Diagnosis of Covid-19. What would be the indication for treatment?

a) Molnupiravir
b) Nirmatrelvir/ritonavir
c) Sotrovimab
d) No indication for treatment

22. State which of the following is an effector function of antibodies:

a) Opsonization of antigens to be phagocytosed.
b) Complement activation by the classical pathway
c) Antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by NK and macrophages
d) All of the above

23. Which of the following answers is true regarding "fold change" in relation to the neutralizing capacity of a drug:

a) It is an absolute number directly related to a drug's neutralizing capacity
b) It is a relative number that refers to the change in the IC50 of a drug with respect to a previous control value
c) It refers to the concentration of drug required to neutralize 50% of the antigen.
d) Refers to the concentration of drug required to achieve 50% of its maximal inhibition

24. Which of the following monoclonal antibodies used against SARS-CoV-2 has a modification to reduce effector function and the potential risk of increased antibody-dependent disease?

a) Sotrovimab
b) Casirivimab-indevimab
c) Tixagevimab-cilgavimab
d) Bebtelovimab

25. What is the circulating Clade of mpox in this pandemic?

a) Clade I (Central Africa)
b) Clade II (West Africa)
c) Clade I (West Africa)
d) Clade II (Central Africa)

26. In people living with HIV infection who are diagnosed with simian smallpox we must take into account:

a) Study of contacts
b) Assess the use of antivirals on an individual basis.
c) If they have poor immunovirological control, they may be at greater risk of complications.
d) All of the above

27. In all but one person with Mpox, the following actions should be performed:

a) Airborne, respiratory, and contact isolation.
b) HIV serology
c) Individualized STI screening
d) Inclusion in PrEP programs after ruling out HIV infection.

28. On which of the following antigens is the classification into Streptococcus pyogenes serotypes based?

a) Wall carbohydrate
b) M membrane protein M
c) Exotoxin
d) Streptolysin

29. The most common age of presentation of current invasive diseases caused by Streptococcus pyogenes in Pediatrics is:

a) Infants
b) Children from 2 to 7 years old
c) Children 7 to 12 years of age
d) Older than 12 years of age

30. The most frequent form of presentation of current invasive diseases caused by *Streptococcus pyogenes* in Pediatrics is:

a) Pneumonia
b) Necrotizing fasciitis
c) Streptococcal Toxic Shock Syndrome (SSTS)
d) Primary bacteremia

31. In relation to the characteristics associated with an increased likelihood of developing a severe necrotizing skin and soft tissue infection, all but one of the following stand out; point it out:

a) Appearance of bullae and/or crepitus.
b) Presence of renal failure and hyponatremia
c) Systemic toxicity and septic state
d) Metabolic alkalosis

32. Which of the following is considered an "anionic" fluoroquinolone with the potential to be active in acidic media and most effective on abscesses and biofilms?

a) Ciprofloxacin
b) Moxifloxacin
c) Delafloxacin
d) Ofloxacin

33. Among the following glycopeptide antibiotics against Gram-positive microorganisms, which one(s) are considered or referred to as "long acting", due to their long and high half-life that achieves prolonged effective antimicrobial activity (more than one week)?

a) Oritavancin
b) Telavancin
c) Daptomycin
d) Teicoplanin

34. Indicate the correct answer regarding the IDSA and ESCMID guidelines in the treatment of infections caused by gram-negative microorganisms.

a) They use similar evidence criteria
b) The IDSA guideline uses criteria based on non-systematic literature reviews.
c) The ESCMID guideline is based on systematic reviews with evidence based on the GRADE system.
d) 2 and 3 are correct

35. Indicate the FALSE answer in relation to the coinciding recommendations, although with nuances, in the targeted treatment of systemic infections by metallobetalactam-producing

a) Enterobacteriaceae in the IDSA, ESCMID and SEIMC guidelines:
b) Cefiderocol is recommended.
c) The association of ceftazidime/avibactam with aztreonam is recommended.
d) Tigecycline is recommended in monotherapy with loading doses and subsequent high doses.
e) Colistin is not recommended

36. Indicate the correct answer regarding the activity of meropem/vabobactam and imipenem/relebactam.

a) They are active against KPC-producing Enterobacteriaceae.
b) Are active against MBL-producing Enterobacteriaceae
c) They are always and equally active against multidrug-resistant P. aeruginosa.
d) Are of choice in infections with carbapenemase-producing Acinetobacter baumannii and Stenotrophomonas maltophilia.

37. Patients receiving CAR T therapy are at increased risk of infection:

a) From post-QMT depletion
b) Prolonged hypogammaglobulinemia
c) Due to the use of corticosteroids in CRS.
d) All are true

38. In the prevention of CAR T. infection:

a) It is essential to perform a good anti-filamentous fungus prophylaxis.
b) It is essential to make a good antibacterial prophylaxis.
c) It is essential to make a rigorous use of catheters and avoid nosocomial infection.
d) It is essential to selectively wash the lymphocytes to be infused.

39. Patients with CAR T who have COVID19:

a) Are potentially very severe patients
b) They present above all significant inflammation
c) They require early and probably combined antiviral treatment.
d) a and c are true

40. At present and globally, what is the approximate percentage of clinical isolates of Pseudomonas aeruginosa resistant to carbapenemens in Spain?

a) 0-5%
b) 5-10%
c) 10-25%
d) 50-75%

41. In general and without taking into account the specific epidemiology of each hospital, what is the most frequent mechanism of resistance of Pseudomonas aeruginosa to carbapenems in our country?

a) Production of carbapenemases
b) Hyperproduction of ampC and loss of porins.
c) Hyperexpression of efflux pumps
d) Siderophore receptor mutation

42. If other clinical data at the moment Which of the following treatments do you consider most appropriate for a bacteremia caused by MIV-producing Pseudomonas aeruginosa?

a) Ceftolozane-tazobactam
b) Cefiderocol
c) Aztreonam
d) Ceftazidime-avibactam

43. Mark the WRONG answer regarding rezafungin:

a) It belongs to the echinocandin family.
b) It can be administered orally
c) It is recommended to be administered once a week.
d) Its spectrum of activity is similar to that of the other echinocandins.

44. Ibrexafungerp is a new antifungal whose main novelty is:

a) Its oral administration
b) Its mechanism of action
c) Its high activity against filamentous fungi.
d) Its authorization by the EMA for antifungal prophylaxis.

45. Which of the following antifungals is not cross-resistant to anidulafungin?

a) Rezafungin
b) Ibrexafungerp
c) Olorophyme
d) All three antifungals are cross-resistant with anidulafungin.

46. Regarding FTIR spectroscopy it is FALSE that:

a) It is an infrared spectroscopy.
b) It can be used for serotyping of *S. pneumoniae*.
c) It can be used as a point-of-care technique for the rapid diagnosis of STIs.
d) Can be used for outbreak detection

47. HIGH LEVEL resistance to cefiderocol is due to:

a) Mutations in the cirA gene (siderophore receptor)
b) Presence of metallo-beta-lactamases, mainly NDM
c) Presence of AmpC and PER type beta-lactamases.
d) The combination of multiple factors

48. In relation to the CRISPR system it is FALSE that:

a) It is a natural adaptive immune system of prokaryotes.
b) It is a system based on artificial intelligence
c) It can be used for the detection of viruses, bacteria, fungi and parasites.
d) It can detect resistance genes and sensitize bacteria to antibiotics.

49. Which of the following drugs is not part of the 24-week treatment regimen against rifampicin-resistant tuberculosis?

a) Linezolid
b) Cycloserine
c) Moxifloxacin
d) Bedaquiline

50. Select the correct answer from the following:

a) The duration of antibiotic treatment of a joint prosthesis infection following any modality of surgery should be 12 weeks.
b) Among the recommendations for the proper use of vascular catheters are femoral cannulation and the use of previous antibiotic prophylaxis.
c) Treatment of ADVP-associated right-sided endocarditis can be reduced from 6 to 2 weeks parenterally with similar efficacy and free of complications.
d) One of the criteria that allows postponing valve surgery until the end of treatment in left-sided endocarditis of AVPD is that it is produced by *S. aureus*.

51. Regarding the cases of invasive fungal infection associated with COVID-19 point out the correct answer:

a) The diagnosis of CAPA (Covid-associated pulmonary aspergillosis) is made like influenza early before 5 days.
b) Risk factors for CAPA are tozilizumab use, dexamethasone use, advanced age, and respiratory distress from Covid requiring mechanical ventilation.
c) Like the Indian cases, the most frequent CAM (Covid-associated mucormycosis) in our environment was rhinocerebral.
d) Among invasive candidiasis (CAC) in COVID patients, the most frequent was *Candida auris*.