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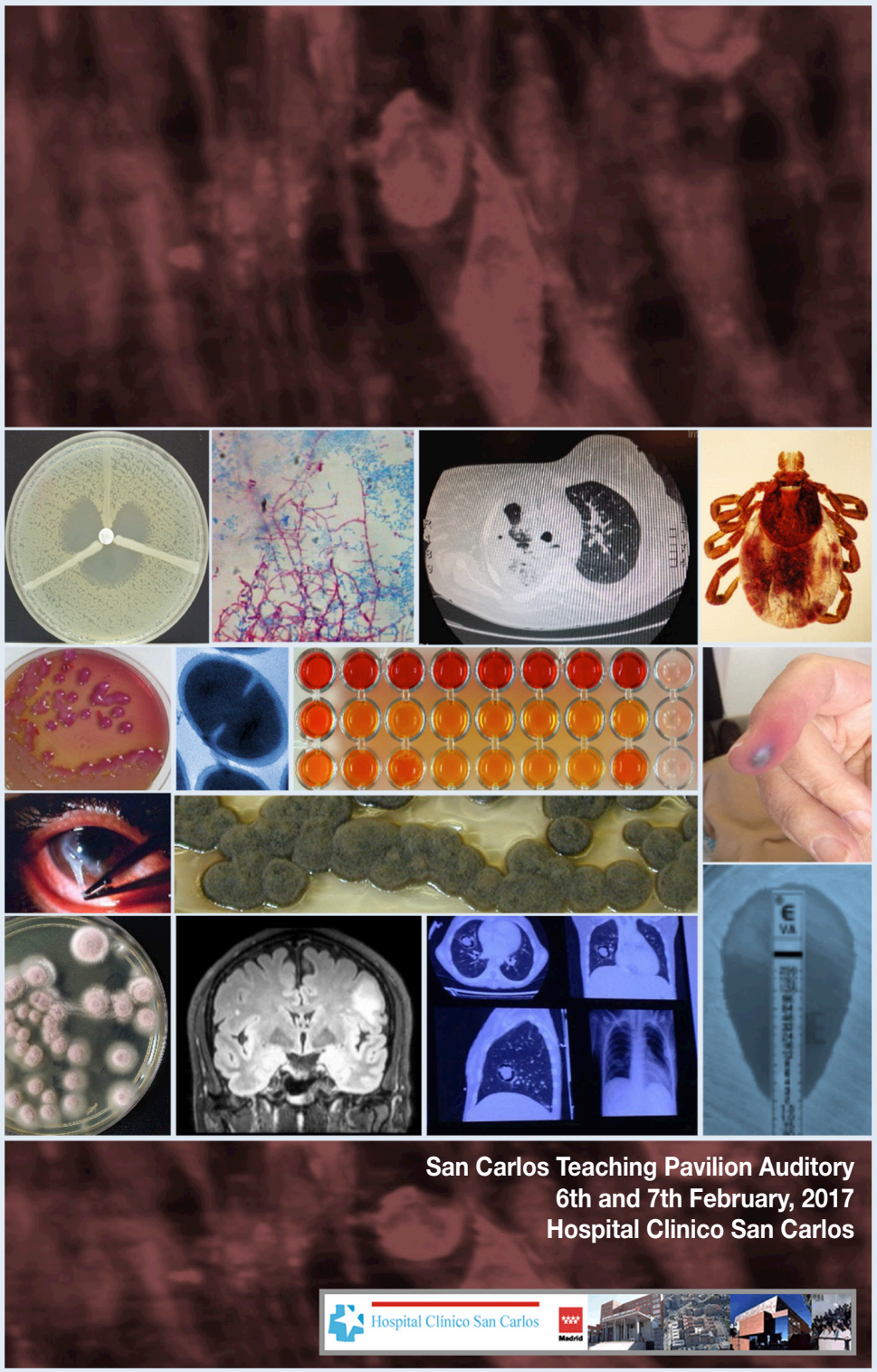

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Introduction

Update in Infectious Diseases 2017

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ABSTRACT

Antimicrobial resistance in complex models of continuous infection is a current issue. The update 2017 course addresses about microbiological, epidemiological and clinical aspects useful for a current approach to infectious disease. During the last year, nosocomial pneumonia approach guides, recommendations for management of yeast and filamentous fungal infections, review papers on the empirical approach to peritonitis and extensive guidelines on stewardship have been published. HIV infection is being treated before and more intensively. The implementation of molecular biology, spectrometry and inmunology to traditional techniques of staining and culture achieve a better and faster microbiological diagnosis. Finally, the infection is increasingly integrated, assessing non-antibiotic aspects in the treatment.

Key words: Infectious diseases, current concepts

Actualización en patología infecciosa 2017

RESUMEN

La resistencia a los antimicrobianos en modelos cada vez más complejos de infección continúa siendo actualidad. El curso de actualización de este año 2017 trata aspectos microbiológicos, epidemiológicos y clínicos útiles para un abordaje actual de la patología infecciosa. Durante el último año se han publicado guías de aproximación a la neumonía nosocomial, recomendaciones sobre el manejo de la infección fúngica por levaduras y filamentosos, documentos de revisión sobre el abordaje empírico de la peritonitis y una extensas guías sobre stewardship. En la infección por el VIH, cada vez se trata antes y más intensamente. La implementación de la biología molecular, la espectrometría y la inmunología a las técnicas tradicionales de tinción y cultivo consiguen un diagnóstico microbiológico mejor y más rápido. Por último, la infección se aborda de forma cada vez más integral, valorando aspectos no antibióticos en el tratamiento.

Palabras clave: Enfermedades Infecciosas, conceptos actuales

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INTRODUCTION

Last January, the VII 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-08829.2/2016, 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). Faced with a multidisciplinary assistance composed of more than 600 trainees and young associates of all specialties related to infection, the teachers made an update of the most relevant aspects on bacteriology, mycology and virology.

Current supplement of the magazine includes summaries of the lectures given in the presential course. It also includes the questionaire that evaluated the students and a sheet of correct answers to contrast results. Revisions have been grouped under headings to guarantee a greater educational character: update in bacteriology, update in HIV, update in mycology, update in main infectious syndromes and current aproach and methods

UPDATE IN BACTERIOLOGY

The increasing prevalence of MDR/XDR *Pseudomonas aeruginosa* isolates was highlighted by Dr Ruiz-Garbajosa as

a cause of concern due to the difficulties of choosing a correct empiric or definitive therapy. The Doctor introduced us into two alternatives for treating complicated intra-abdominal infections and complex urinary tract infections. In different studies, ceftolozano-tazobactam has proved more active against MDR/XDR *P. aeruginosa* than meropenem, piperacilina-tazobactam or cefepime[1,2], as well as showing MIC ≤ 8 mg/L[2]. The other alternative presented was ceftazidime-avibactam which increases the antipseudomonal activity of ceftazidime by 10%[3].

In spite of being hidrolized by metallo-betalactamases and as the main mechanism of resistance in Spain, it is the accumulation of chromosomal mutations; these two antibiotics can be taken into account when deciding to treat.

UPDATE IN HIV

HIV infection continues being an almost incurable condition and patient management is an intensely researched topic. A team from Hospital Universitario Ramón y Cajal led by Dr Moreno presented a selection of articles, an update of guidelines particularly relevant to patient care and clinical practice. They stressed the relevance of the 2015 START study[4]. It established that antiretroviral (AR) therapy should be initiated as soon as possible, even with decent (>500 cells/mm^3) CD4 count. A deep analysis of the data found that the patients who benefit the most are those with the higher risk. Namely, age 50 or higher, over 50.000 RNA copies/mm^3, <0.5 or more in CD4/CD8 ratio and (high) Framingham score at 10 years (over ten). Studies that evaluate the efficacy of dolutegravir, an integrase inhibitor, in mono and double therapy also were commented. The PADDLE study[5] found that combined therapy with dolutegravir and 3TC in AR naive patients was successful in reaching undetectable (<50 copies/mm3) viral load. Whereas dolutegravir monotherapy lead to virological failiure and development of resistance mutations[6]. Finally, an analysis was made on the evolution of AR therapy guidelines, finding a trend towards being more restrictive, limiting the preferred regimens to those based on integrase inhibitors, placing protease inhibitor and non nucleoside based regimens as alternative regimens with few exceptions[7].

UPDATE IN MICOLOGY

Increasing risk of patients suffering invasive fungal infection (IFI) with high mortality rates led Dr. Peman to introduce us into the latest diagnostic advances in invasive candidiasis and IFI caused by molds. Although the blood culture remains the gold standard method to diagnose candidemia, its final identification by traditional methods (such as Vitek or ChromAgar) concludes in an estimated time of 61 hours. MALDI-TOF, PNA-FISH and multiplex-PCR platforms provide reduced identification times with better antifungal therapy management[8]. While these methods rely on positive blood culture, T2 magnetic resonance can be performed in non-incubated blood and would take in up to 4 hours in patients with invasive candidiasis and ungrounded blood cultures, having a significant impact on antifungal therapy, resistances and healthcare costs[9] .

Novelties in IFI caused by molds diagnosis include international standardization of PCR techniques and their combination with galactomannan for a relative risk reduction of 68.1% in invasive aspergillosis diagnosis[10]. In the diagnosis of other filamentous fungus, PCR amplification followed by Electrospray Ionization/Mass Spectrometry have shown promising results[11]. Additionally, Volatile Organic Compounds biomarkers in exhaled breath could bring a new non-invasive method for clinical diagnosis that would avoid using invasive techniques such as bronchial biopsy.

On the topic of invasive candidiasis in the neutropenic patient, Dr. Fortún reviewed the results of the Spanish CANDIPOP study which confirmed that mortality rates at 1 month were similar both in patients with oncologic-hematologic conditions and in the general population (30 %). This study also showed that the independent factors associated with mortality in the hematologic patient were the same to those found on general population with the exception of a higher incidence of neutropenia and mucositis and a less frequently catheter-associated candidemia[12]. Moreover, Dr Fortún highlighted that, although *Candida albicans* and *Candida parapsilosis* remain as the principal etiological agents in overall, endogenous species such as *Candida tropicalis*, *Candida glabrata* and *Candida krusei* are much more prevalent in the hematological patient[13]. The increased mortality associated with these three species may be due to its greater virulence or its greater resistance to azoles. Nevertheless, the correlation between a severely-affected inmunological status and the isolation of these species makes it difficult to distinguish the species-dependent mortality from the host-dependent mortality.

The recommendations on treatment of invasive candidiasis and candidemia in the hematological patient were also covered, specially the key role of echinocandins as first-line treatment in neutropenic patients due to its beneficial safety profile[14], leaving lipid amphotericin B as an alternative because of its greater toxicity. In the specific case of C. krusei isolation, the treatment with either echinocandins, liposomal amphotericin B or voriconazole was strongly recommended. With respect to treatment duration and, despite low level of evidence, a two-week cycle was recommended if candidemia is controlled, there is no distant foci and the clinical improvement is evident. Since the origin of the candidemia in the neutropenic patient may be endogenous and not vascular, the need of addressing the source of candidemia before catheter withdrawal was emphasized. The neutrophil transfusion was also approached, however, the lack of strong evidence from available studies holds it as a last resort in neutropenic patients.

In 2016 appeared the new IDSA guidelines for the diagnosis and management of invasive aspergillosis (IA)[15] after eight years since the last edition. According to these new guidelines, in patients with strongly suspected IA, antifungal therapy

should be warranted while a diagnostic evaluation is conducted. Regarding treatment, voriconazole remains the antifungal of choice although with the same level of evidence as isavuconazole[16]. Combined voriconazol (300mg/12h as initial doses) with an echinocandin has also been positioned as a first-line option[17]; leaving liposomal amphotericin B for cases in which azole can not be used. Concerning patient follow-up, galactomannan is the biomarker of choice[18], just like pharmacological monitoring. Finally, in the case of breakthrough aspergillosis they recommend, adjusting the dose of azole if it was insufficient, performing a CT and fibrobronchoscopy in order to detect resistant fungi, changing the antifungal agent family and reducing immunosuppression as much as possible.

UPDATE IN MAIN INFECTIOUS SYNDROMES

In 2016 the ATS guidelines[19] for the management of adults with hospital-acquired pneumonia were published. This is the second hospital infection in order of prevalence and with high morbidity and mortality rates[20]. This new edition bases the empirical treatment recommendation on two factors, the risk of multiresistance determined exclusively by the prior use of intravenous antibiotics, and the severity of the underlying disease. Thus, a careful reading is needed, as some of the recommended empirical treatments seem to have forgotten the aspiration etiology, the high rates of quinolone resistance in some regions[21] and the limitations in the use of vancomycin in certain patients. Furthermore, some new antibiotics, which could be useful in patients with infectious like these, have been approved recently: antipseudomonic activity of ceftolozane-tazobactam, activity against methicillin-resistant *Staphylococcus aureus* (MRSA) of ceftaroline, inhibition of several carbapenemases by ceftazidime-avibactam, the lower adverse events of tedizolid and the advantageous dosage of dalbavancin.

Intra-abdominal infection (IAI) is the main cause of post-operative morbidity after abdominal surgery and the most frequent cause of admission to post-surgical critical care units. Dr. Maseda provided prevalence data of extended-spectrum beta-lactamase (ESBL) resistance of Enterobacteriaceae[22], as an important aspect when establishing the treatment of IAI. He also indicated risk factors for infection/colonization by *Enterococcus* spp., *P. aeruginosa* and *Candida* spp. Regarding treatment of IAI, a standard regimen is the combination of β-lactams with β-lactamase inhibitors, such as piperacillin-tazobactam. ESBL-producing strains have shown resistance to this antibiotic, being carbapenems the antibiotics of choice in these cases. The role of the new combinations, ceftolozane-tazobactam[23] and ceftazidime-avibactam[24] in peritonitis, is still under study but appears to have promising results when combined with antibiotics that are active against anaerobes and enterococci and/or MRSA. Empiric antimycotic therapy with echinocandins is indicated in patients with secondary peritonitis of nosocomial origin and tertiary peritonitis, with subsequent de-escalating to azole once the susceptibility of the isolate is available[25].

Dr. Padilla reviewed the most important aspects of nosocomial urinary tract infection (UTI). This is the third most common cause of infection in admitted patients, with catheter-associated UTI being of special importance. Data were presented on the relevance of limiting the insertion of unnecessary catheters and reducing the duration of catheterization as prevention strategies[26]. Regarding etiology, *Escherichia coli* remains the most common causal agent in uncomplicated cystitis and pyelonephritis and complicated UTI. Also, the role of *P. aeruginosa* in the etiology of secondary bacteremia was highlighted[27]. Regarding treatment, Dr. Padilla pointed out cases in which asymptomatic bacteriuria should be treated[28], with the aim of limiting unnecessary treatments and avoiding the selection of MDR microorganisms. In addition, she explained that treatment must be conducted following certain criteria such as risk factors of severity and local epidemiology (risk of MDR).

Implantation rates of vascular prothesis, grafts and implantable cardiac electronic devices (IECDs) are increasing in developed countries. Dr. Jose Luis del Pozo from "Clinica Universitaria de Navarra" presented his expertise on the subject. Contributing factors are, on the supply side, wider eligibility criteria, advances in surgical techniques and graft design, high prevalence of cardiovascular diseases, aging population on the demand side. Likewise device implantation, incidence of infection is also increasing[29]. Consistent risk factors for infection in IECD include lack of antimicrobial prophylaxis, number and complexity of procedures and *S. aureus* nasal colonization and groin incision for vascular grafts. The infective microorganisms are predominantly biofilm producing coagulase negative staphilococci and *S. aureus*. Diagnosis is based on clinical symptoms, compatible CT scans, echocardiography and microbiological findings in blood culture and tissue samples. CT/PET fusion imaging may be indicated if previous radiologic exams are indeterminate[30]. Treatment options are dependent on the patient´s comorbilities and general health condition. Extraction of infected material and reconstruction is the recommended option followed by 2 weeks of antibiotic therapy. If impossible, 6 weeks of antibiotic i.v. therapy, maintaining the IECD is the headstone of treatment. For exceedingly frail or terminally ill patients chronic suppressive antibiotic therapy might be the best option[31].

CURRENT APPROACH AND METHODS

Over the last few years there have been important changes in the definition of sepsis, septic shock and its diagnostic criteria. Dr. González del Castillo described these changes on the prognostic aspect to identify patients at risk of a poor short-term outcome; analyzing the most important recently published studies; the causes that triggered the need to redefine this syndrome; and the controversy that has emerged as a result.

The new definition states that sepsis is a potentially life-threatening organic dysfunction, caused by a dysregulated host response to infection[32]. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular,

and metabolic abnormalities are associated with greater risk of mortality[32]. In addition, extensive databases were retrospectively analyze and it was concluded that SOFA was the most appropriate score to diagnose sepsis and to prognose mortality compared to other different known scores (SIRS, LODS)[33]. The inconvenience with SOFA score is that this scale contains analytical variables, which could determine a delay in diagnosis and in the start of treatment. For this reason, these updated definitions are accompanied by a new screening tool, known as qSOFA (respiratory rate>= 22rpm, altered level of consciousness and systolic blood pressure <= 100 mmHg).

However, this score has led to some controversy due to its lower sensitivity than the Systemic Inflammatory Response Syndrome criteria (SIRS), previously used to identify patients at risk, even though they show a similar negative predictive value (NPV)[34]). As it is a simpler score and can be performed at any level of care, it was concluded that qSOFA should replace SIRS as a screening tool. We can conclude that these updated definitions and clinical criteria should facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing it. Nevertheless, Dr. González del Castillo suggested that we should not forget that there is still a long way to go in this topic, this process remains a work in progress.

Nowadays, increasing resistance is a real problem that we have to face, the earlier the pathogen and resistant patterns are identified, the lower spectrum of antibiotics will be required[35]. That is the reason why Dr Emilia Cercenado sets out how to manage and combine ``old´´, rapid and new techniques. Depending on the infection site, and focusing on the severe infections, there are plenty of new molecular assays for detection of bacteria, fungi or viruses. For bloodstream infections, for example, one of the most impressive is the new nanodiagnostic approach, T2 magnetic resonance assay for the rapid diagnosis of candidemia[36]. Focused on intensive care units, rapid microbiological techniques for diagnosing catheter-related bloodstream infections (CR-BSI), hospital-acquired pneumonia, and especially, ventilator-associated pneumonia (VAP) or skin and soft-tissue infections had been presented. Nucleic acid assays are becoming the test of choice[37], in addition to pathogen identification also for detecting the resistance patterns in few hours. Nevertheless, we should not forget old techniques as cultures, direct antimicrobial susceptibility testing, and Gram staining as they are the gold standard, as well as the biomarkers.

The rapid emergence of multidrug-resistant bacterias is occurring worldwide and is one of the main and most serious problems and challenges in the Public Health Agenda all around the world. Dr. Paño-Pardo proposed several clues to improve antimicrobial prescribing in a very original way. The main ideas were organized in a practical Decalogue, mainly stating that since antibiotic prescribers are the workforce to achieve better antimicrobial use, educational activities targeting prescribers are among the most valuable resources of Antimicrobial Stewardship programs (ASP).

The main principles proposed can be summarized as follows: antibiotics should be avoided when there is no evidence or high suspicion of a bacterial/fungal infection; in severe infections it is advisable to start the antibiotic as soon as possible; prescribers should choose empiric therapy considering local epidemiology and patients´ individual factors; it is important using PK/PD (pharmaco-kinetic and pharmaco-dynamic properties) models to predict clinical and bacteriological efficacy and to help identify the most suitable dosage; correct sampling of specimens for culture, as well as its processing, are essential to achieve an etiological diagnosis and facilitates targeted therapy; samples should be obtained prior to the beginning of the antibiotic treatment (if possible); documenting the antibiotic plan is among the most widely accepted quality indicators for antimicrobial prescribing[38,39]; antibiotic therapy should be reassessed periodically (each 48-72 hours); as soon as possible, we must switch to oral treatment when the syndrome and the microorganism allows it, and finally, antibiotic treatment duration should be as short as possible. These principles, if correctly applied, could contribute to obtain the best possible outcomes from antimicrobial therapy.

Hospital at Home (HaH) is a healthcare modality that extends the monitoring and treatment of acute infectious proccesses and chronic pathology descompensations deploying an antimicrobial therapeutical arsenal similar to that applied on hospitalized patients. There is enough evidence in the literature supporting its clinical efficacy and safety and the associated reduction in mortality, re-entry rates and derived costs[40]. However, in Spain, the implantation of HaH services is irregular, with only one out of every 7 acute hospitals incorporating it. Moreover, only 48% of those units offer coverage to all of their reference population. Thus, only the 2% of all the hospitalization episodes registered in Spain in 2013 were treated through HaH[41].

HaH is particularly useful in the treatment of some hospital-sustainability problems such as nosocomial infections. In this regard, outpatient parenteral antimicrobial therapy (OPAT) was firstly used as an option for non-life-threatening infections requiring long-term parenteral antibiotic treatment such as osteomyelitis, septic arthritis, soft tissue infections and respiratory infections in patients with cystic fibrosis. However, the emergence of more effective, safe and long-lasting antibiotics has allowed the expansion of this therapeutical approach to practically any infection. Nevertheless, the safety and efficacy of OPAT relies on the correct selection of the patient and its infectious process, the prescribed antimicrobial agent, the venous access route and the infusion devices and modalities.

Nosocomial infections imply an extension of the hospital stay often requiring long intravenous treatments without any effective oral alternatives. As Dr González Ramallo highlighted, the recent introduction of some antibiotics against multidrug-resistant organisms suitable for outpatient intravenous therapy, have rendered HaH units as an effective and safe care tool for the treatment of nosocomial infections. In a prospective observational study carried out in a Spanish HaH unit from 2008 to 2012, a total of 433 infections caused by multidrug-resistant bacteria were treated intravenously at home[42].

Regarding economic savings, a recent economic study carried out by Dr González Ramallo's group in 3 Spanish centres[43] pointed out that, in comparison with conventional hospitalization, the use of OPAT in the context of HaH could cut off more than 80% of the costs derived from each stay.

As the rise of antimicrobial resistance threats conventional treatment of bacterial infections, Dr. Salavert highlighted the role that new non-antibiotic therapeutic approaches might play in the future. Anti-virulence strategies aim to make it easier for the immune system to overcome infections by interacting with virulence factors, like preventing biofilm formation or interfering quorum-sensing signaling. Phages may rise as a potential complement to current antimicrobial chemotherapy due to their high specificity and safety (it does not possess affinity to eukaryotic cells), but there are serious concerns about the development of bacterial resistance, their restrictive specificity and DNA integration efficacy. Vaccines have also originated interest for infection prophylaxys, with *Clostridium difficile* vaccine achieving the greater progress so far, showing to be safe and immunogenic[44]. While main application of microbiome medicine has been treating recurrent infections caused by *C. difficile*[45], probiotics and fecal microbiota transplantation could help to preserve normal microbioma and prevent growth of pathogenic bacteria[46,47]. While it is unlikely that alternative therapies will displace the need for new antibiotics in short and medium term, with sufficient funding, these new treatments might replace or supplement antibiotics in the long term.

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Epidemiology of antibiotic resistance in *Pseudomonas aeruginosa*. Implications for empiric and definitive therapy

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ABSTRACT

Pseudomonas aeruginosa is one of the major pathogens causing hospital-acquired infections. It can easily develop antibiotic resistance through chromosomal mutations or by horizontal acquisition of resistant determinants. The increasing prevalence of multi-drug-resistant (MDR) or extensively-drug-resistant (XDR) *P. aeruginosa* isolates is associated with the dissemination of the so-called high-risk-clones, such as ST175. Infections caused by MDR/XDR are a cause of concern as they compromise the selection of appropriate empiric and definitive antimicrobial treatments. Introduction of new antibiotics with potent activity against MDR/XDR *P. aeruginosa* opens new horizons in the treatment of these infections.

Key words: *P. aeruginosa*, multidrug-resistance, ceftolozane-tazobactam

Epidemiología actual de la resistencia en *Pseudomonas aeruginosa*. Implicaciones en la terapia empírica y dirigida

RESUMEN

Pseudomonas aeruginosa es uno de los principales patógenos nosocomiales. Presenta una gran capacidad para desarrollar resistencias, bien por mutaciones cromosómicas o por adquisición de genes localizados en elementos transferibles. La emergencia de *P. aeruginosa* multirresistente (MR) y extremadamente resistente (XR) se ha asociado con la diseminación de los denominados clones de alto riesgo, como el ST175. Las infecciones causadas por estos clones comprometen la adecuación del tratamiento antimicrobiano empírico y definitivo. La introducción de nuevos antibióticos con potente actividad frente a *P. aeruginosa* MR/XR abre nuevos horizontes en el tratamiento de estas infecciones.

Palabras clave: *P. aeruginosa*, multirresistencia, ceftolozano-tazobactam

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INTRODUCTION

Pseudomonas aeruginosa is a non-fermentative gram-negative bacteria with an extraordinary ability to colonize a large variety of ecological niches, particularly moist environments. Currently, *P. aeruginosa* is one of the major pathogens causing hospital-acquired infections, in particular affecting patients with impairment of immune defences or admitted in the Intensive Care Unit (ICU)[1,2]. This organism is not only intrinsically resistant to a wide range of antimicrobials, but also has an extraordinary capacity for developing resistance to commonly used antimicrobials through the selection of mutations in chromosomal genes or by horizontal acquisition of resistant determinants. The increasing prevalence of multidrug-resistant (MDR) strains is a cause of concern as it compromises the selection of appropriate empirical and definitive antimicrobial treatments. This situation is associated with worse outcomes and higher mortality, particularly in patients with severe *P. aeruginosa* infections, including bacteraemia and ventilator associated pneumonia[3].

EPIDEMIOLOGY OF *P. aeruginosa* IN THE HOSPITAL SETTING

The European Centre for Disease Prevention and Control 2011-2012 Point-Prevalence Survey for health-care associated infections (HCAIs) found that almost 9% of all infections were caused by *P. aeruginosa*, and that it was the fourth most common pathogen in European hospitals[1]. Similar data was reported in a survey conducted by the Centers for Disease Control and Prevention in 2011, which found that 7.1% of HCAIs were caused by *P. aeruginosa* in the United States[2]. In

Spain, the 2016 EPINE survey found that *P. aeruginosa* was the second cause of hospital-acquired infections, and that it represented 10.5% of all these infections[4]. This prevalence is higher in the ICU setting, for instance the 2016 ENVIN-HELICS survey conducted by the Spanish Society of Intensive Care Medicine reported a 13% prevalence of *P. aeruginosa* infections[5].

Depending on the infection site, *P. aeruginosa* is one of the leading causes of ventilator-associated pneumonia (VAP), followed by bloodstream and urinary tract infections[1,2,4]. In ICUs in Spain, *P. aeruginosa* is the first cause of VAP, accounting for almost 21% of episodes[5].

EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE MECHANISMS IN *P. aeruginosa*

P. aeruginosa is intrinsically resistant to a wide range of antimicrobials mainly due to low outer membrane permeability, the expression of efflux pumps and the production of an inducible AmpC cephalosporinase. Moreover, it can also easily develop resistance to antimicrobials commonly used in the treatment of *P. aeruginosa* infections such as piperacillin/tazobactam, ceftazidime, carbapenems, fluoroquinolones or aminoglycosides. According to the data reported by The European Antimicrobial Resistance Surveillance Network (EARS-Net) in 2015, the mean resistance percentages among *P. aeruginosa* invasive isolates for piperacillin/tazobactam, carbapenems and fluoroquinolones were close to 20%, while for ceftazidime and aminoglycosides they were 13%[6]. An increasing trend for piperacillin/tazobactam resistance was observed in Europe between 2011 and 2015, while carbapenem and ceftazidime resistance remained stable during this period[6]. Nevertheless, important variations in resistance rates were described in the different European countries, with higher resistance rates in the southern and eastern countries compared with the northern countries[6]. A multicentre study including *P. aeruginosa* isolates recovered from bloodstream infections from Spanish hospitals reported higher resistance rates for piperacillin/tazobactam, ceftazidime, fluoroquinolones and aminoglycosides (with the exception of amikacin) than those reported by EARS-Net[6,7]. However, carbapenem resistance was similar to that described by EARS-Net[6,7]. Sader et al in the SENTRY surveillance program found a moderate *in vitro* activity of piperacillin/tazobactam, ceftazidime and carbapenems against *P. aeruginosa* respiratory isolates collected from hospitalized patients with pneumonia US and European hospitals[8]. Moreover, resistance rates were higher in European than in US hospitals[8]. Amikacin and colistin were the most active antibiotics against blood and respiratory *P. aeruginosa* isolates[7,8] (table 1).

On the other hand, the prevalence of MDR *P. aeruginosa* has increased in the last decade reaching values of 30% in some areas, such as in eastern European countries[9]. A considerable proportion of MDR strains meets the criteria of XDR, which is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories[6]. A multicentre study on

Table 1 **Antimicrobial susceptibility of *P. aeruginosa* isolates recovered from patients with bloodstream infections and pneumonia**

	Blood isolates[a] (%R)[c]	Respiratory isolates[b] (%R)[c]	
Antimicrobial agent	Spanish hospitals (n=190)	EU hospitals (n=1,250)	USA hospitals (n=1,439)
Piperacillin/tazobactam	27.9	36.1	27.1
Ceftazidime	23.7	31.3	20.4
Cefepime	38.4	27.9	19.6
Imipenem	22.6	-[d]	-[d]
Meropenem	15.2	14.4	9
Ciprofloxacin	28.4	-[d]	-[d]
Levofloxacin	31.6	36.6	29.5
Gentamicin	21.1	24.8	13
Tobramycin	18.4	23.1	8.3
Amikacin	1.6	11.2	3.8
Colistin	1.1	1	1.1

[a]Data adapted from Cabot G et al.[7]

[b]Data adapted from Sader HS et al.[8]

[c]Percentage of resistant isolates according to EUCAST criteria

[d]Antimicrobial not tested

P. aeruginosa bloodstream infections in Spain found that 15% of the isolates were XDR[9]. Moreover, the EARS-Net reported a significant increase in Spain of invasive isolates with combined resistance to three or more antimicrobial groups (piperacillin–tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), with rates ranging from 4% in 2005 to 14% in 2015[6]. Among XDR strains the polymyxins and amikacin were the antimicrobials that retained higher activity[6,9].

The mutational-mediated mechanisms, especially the hyperproduction of the chromosomally encoded AmpC betalactamase, the repression or inactivation of the carbapenem porin OprD, or the upregulation of efflux pumps are the main mechanisms involved in the development of antibiotic resistance in *P. aeruginosa*. Thus, the emergence of XDR or MDR strains is usually a consequence of the accumulation of several of these chromosomally mediated resistance mechanisms in the bacteria[7,9]. In addition, the acquisition of plasmid-mediated resistance genes coding for carbapenemase enzymes is an increasing problem in *P. aeruginosa*[7,9]. The metallo-betalactamases (MBLs) are the most commonly detected carbapenemases in *P. aeruginosa*, with VIM and IMP types being the most widely distributed[9]. Class A carbapenemases (mainly KPC type) are less frequent, but have been documented to be widespread in certain geographical areas, particularly in South America[9].

Data on the current prevalence of *P. aeruginosa* producing carbapenemase are scarce due to superimposed resistance phenotypes with other resistance mechanisms. Antibiotic resistance surveillance studies in Spain showed that the prevalence of carbapenemase producing isolates has increased from 0.08% in 2003 to 2.7% in 2009, with a predominance of VIM enzymes[10,11]. *P. aeruginosa* producing carbapenemase isolates are also associated with MDR or XDR phenotypes. Thus, the detection of carbapenemase production in *P. aeruginosa* is important for not only for the adequate selection of antimicrobial therapy but also for hospital epidemiology surveillance and infection control.

POPULATION STRUCTURE OF MDR/XRD *P. aeruginosa*

Molecular epidemiology studies of antibiotic susceptible *P. aeruginosa* isolates from hospital origin have described a highly polyclonal population[9]. However, the emergence of MDR/XDR *P. aeruginosa* revealed the existence of interhospital-disseminated MDR/XDR clones, denominated as high-risk clones (HRCs). The ST111, ST175, and ST235 clones have been described as the most successful *P. aeruginosa* HRCs, grouping the majority of MDR/XDR strains[9]. The ST111 and ST235 HRCs show a worldwide distribution, while ST175 clone is confined to European countries[9]. A wide dispersion of XDR *P. aeruginosa* belonging to ST175 clone has been found in Spanish hospitals[12,13]. In the majority of these strains the mutational mechanisms were responsible for the XDR phenotype, although hospital outbreaks of ST175 *P. aeruginosa* producing VIM-2 or VIM-20 have also been reported[9,12,13].

NEW ALTERNATIVES FOR THE ANTIBIOTIC EMPIRICAL AND DEFINITIVE TREATMENT OF MDR/XRD *P. aeruginosa*

The inappropriate empirical antibiotic therapy of MDR/XRD *P. aeruginosa* infections has been associated with increased mortality, length of hospital stay and increased hospital costs[2]. Antibiotic combinations are frequently used for the treatment of these infections, although the value of combination therapy compared to that of monotherapy remains controversial[2]. Moreover, amikacin and colistin are among the antipseudomonal antibiotics with greatest coverage against MDR/XRD *P. aeruginosa,* but both of them are associated with side effects and toxicity. In this scenario, new antibiotics with activity against MDR/XRD *P. aeruginosa* have been developed, and they represent an accurate alternative option for the treatment of infections produced by this organism.

Ceftolozane/tazobactam is an antibacterial consisting of ceftolozane, a novel antipseudomonal cephalosporin, with tazobactam, a well-established betalactamase inhibitor, that has been recently approved for the treatment of complicated intra-abdominal infections (plus metronidazole) and complicated urinary tract infections. The addition of tazobactam did not produce significant enhancement of the *in vitro* activity of ceftolozane against *P. aeruginosa* isolates, but enhanced the coverage of Enterobacteriaceae isolates producing extended-spectrum betalactamases. Ceftolozane has demonstrated potent *in vitro* activity against *P. aeruginosa* ($MIC_{50/90}$, 0.5/4 mg/L) and in different studies has shown higher activity compared with piperacillin/tazobactam, ceftazidime or meropenem[14,15]. More than 90% of clinical *P. aeruginosa* isolates show an MIC ≤ 8 mg/L[15]. Ceftolozane/tazobactam remains active against the majority of MRD/XDR isolates ($MIC_{50/90}$, 4/>64 mg/L), since it is not affected by some of the main resistance mechanisms in *P. aeruginosa* (AmpC hyperproduction, efflux pumps and/or loss of OprD) (figure 1)[14,15]. *In vitro* studies have demonstrated that the development of ceftolozane/tazobactam resistance is much slower than that of resistance to other antipseudomonal agents (ej. ceftazidime)[16]. In spite of the good antipseudomonal activity of ceftolozane/tazobactam, this is hydrolysed by carbapenemases such as metallo-betalactamases (MBLs). However, in Spain, since accumulation chromosomal mutations are the main mechanism responsible for MDR/XRD phenotypes, ceftolozane/tazobactam is a suitable therapeutic option in the current epidemiological scenario, not only for definitive therapy but also for empiric therapy.

Ceftazidime/avibactam, another new antibiotic with antipseudomonal activity, has also been approved for the treatment of complicated intra-abdominal infections (plus metronidazole) and complicated urinary tract infections. It is the combination of a third-generation antipseudomonal cephalosporin with the novel non-betalactam betalactamase inhibitor avibactam. Avibactam inhibits class A (ESBL and KPC), class C (AmpC) and some class D (such as OXA-48)

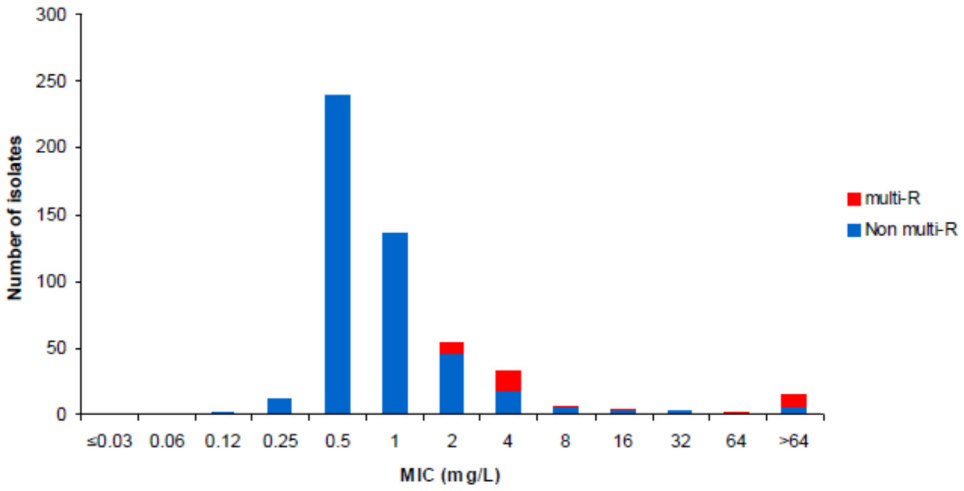

Figure 1 | **Activity of ceftolozane/tazobactam remains in *P. aeruginosa* with and without multidrug resistance phenotype recovered in Spain (data obtained from reference 14)**

betalactamases. Unfortunately, avibactam dose not inhibit MBLs. Furthermore, the addition of avibactam to ceftazidime increases the antipseudomonal spectrum of the latter by approximately 10%[17]. Ceftazidime/avibactam inhibited 82% and 76% of MDR and XDR strains at CMI ≤8 mg/L, respectively[17]. As with ceftolozane, ceftazidime/avibactam is not active against *P. aeruginosa* producing MBLs.

In summary, ceftolozane/tazobactam and ceftazidime/avibactam are new alternatives with potential to improve outcomes of patients with MDR/XDR *P. aeruginosa* infections. Prevalence of different resistance mechanisms in *P. aeruginosa* influences the positioning of ceftolozane/tazobactam or ceftazidime/avibactam for empiric use in infections due to this organism. Moreover, since carbapenemase production in *P. aeruginosa* is being increasingly reported, the screening of this resistance mechanism in MDR/XRD strains would be indicated or mandatory before starting definitive therapy with these new antibiotics.

CONFLICT OF INTEREST

RC has participate in educational programs organized by AstraZeneca and MSD and had a research project founded by Cubist.

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Highlights in HIV, 2016

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ABSTRACT

Research in HIV-infection continues to grow every year. Reports published in journals or presented at conferences in 2016-2017 have brought light to some issues that had been highly debated. We have selected three conceptual publications, which we find include important information for clinicians taking care of HIV-infected patients.

Key words: HIV, antiretroviral treatment, guidelines

Lo más destacado en VIH, 2016

RESUMEN

La investigación en infección por VIH continúa creciendo cada año. Los artículos publicados en revistas o presentados en conferencias en 2016-2017 han traído luz a algunos aspectos importantes de la enfermedad muy debatidos. Hemos seleccionado tres publicaciones conceptuales, que creemos incluyen información importante para los médicos que cuidan de pacientes infectados por VIH

Palabras clave: VIH, tratamiento antirretroviral, recomendaciones

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Research in HIV-infection continues to grow every year. Despite the enormous progress in different fields of the disease, there are still gaps in the knowledge of given areas relevant for the adequate management of patients. Reports published in journals or presented at conferences in 2016-2017 have not been an exception, as they have brought light to some issues that had been highly debated.

We have selected three publications, which we find include important information for clinicians taking care of HIV-infected patients. No question, other papers equally deserve being in this selection, but these have been our choice. We hope readers will find this information useful for the clinical practice.

START STUDY: THOSE IN MOST NEED ARE THOSE BENEFITING THE MOST

The START Study was presented and published for the first time in 2015[1]. The study has been a hallmark in HIV medicine, as it established the benefits of initiating early antiretroviral therapy, i.e. in patients with a CD4 count greater than 500 cells/mm^3. The clinical trial included patients with more than 500 CD4 cells/mm^3, who were randomized to initiate treatment immediately following randomization (the Immediate ART group) or to defer ART until de CD4 count declined to <350 cells/mm^3 or AIDS developed (the Deferred ART group). The primary composite endpoint was the development of serious AIDS or death from AIDS and/or the development of serious non-AIDS events and death not attributable to AIDS. The results were conclusive showing that the Immediate ART Group developed significantly less events, including both serious AIDS and serious non-AIDS events. Since the results of the START trial were presented, all the antiretroviral treatment guidelines have recommended to initiate treatment as soon as possible after the diagnosis. There is no reason to defer treatment, but there is some associated risk

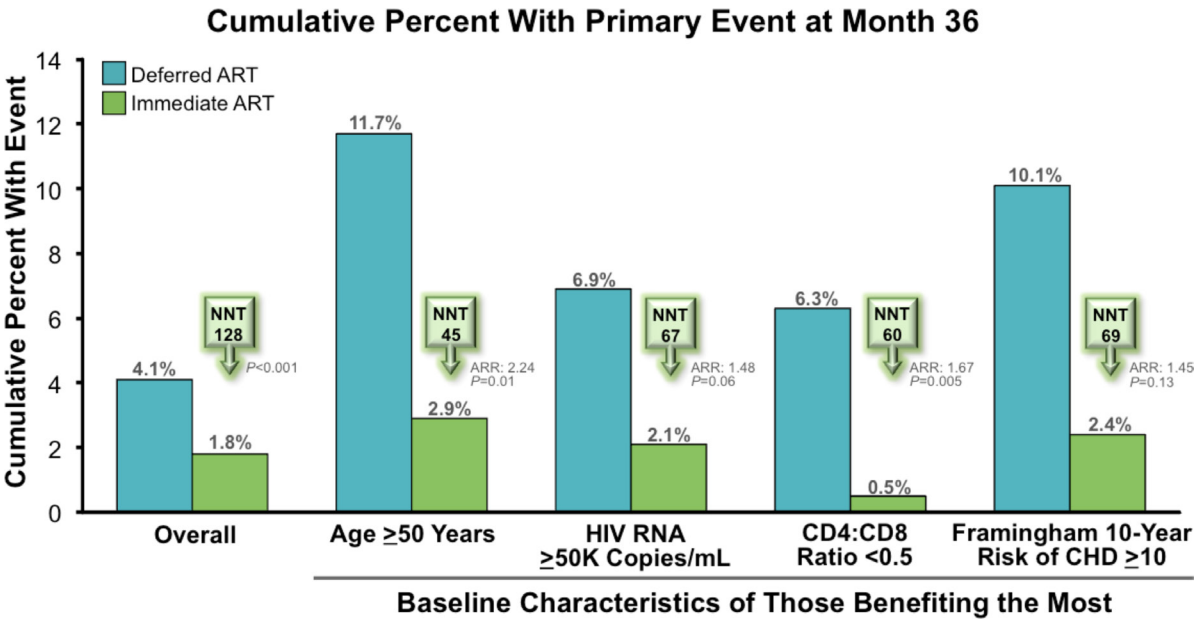

Figure 1 | **START Trial: Cumulative percentage with primary event at month 36.**

NNT: number needed to treat to prevent 1 primary event.
ARR: adjusted rate ratio (deferred-immediate ART).

In this new analysis of the START trial, the authors have investigated what subgroups of patients benefit the most from an early initiation of treatment[2]. Again the results are conclusive: those with the higher risk benefit the most. The baseline characteristics of those benefiting the most included age ≥50 years, HIV RNA ≥50,000 copies/mL, CD4:CD8 ratio <0.5 and a Framingham score at 10 years of ≥10 (figure 1). The number of patients needed to treat to avoid a serious event ranged from 45 in patients older than 50 to 69 in patients with a high Framingham score.

These results highlight the fact that, even with a relatively good immunological status, every HIV-infected patient would benefit of initiating ART, especially if some other characteristic put them at risk for any kind of event.

MORE WITH DOLUTEGRAVIR: TOWARDS THE MINIMALISM

Dolutegravir is an integrase inhibitor that has a higher genetic barrier than previous drugs within the class. Clinical trials have shown that no resistance mutations are selected after virological failure with dolutegravir containing regimens in patients without prior antiretroviral treatment and no integrase-associated mutations. This characteristic, together with a high intrinsic antiviral potency, has prompted investigators to evaluate the administration of the drug in single or dual regimens.

The PADDLE study assessed the efficacy of a dual regimen consisting of 3TC plus dolutegravir in antiretroviral-naïve patients[3]. Inclusion criteria were a CD4 count greater than 200 cells/mL and a viral load lowen than 100,000 copies RNA HIV/mL. All the 20 patients analysed had undetectable viral load (<50 copies/mL) at 24 weeks (primary endpoint), including 4 patients who had a viral load >100,000 copies/mL at baseline. The success of this pilot trial has been the basis for two phase III clinical trials using the combination of 3TC/dolutegravir, as initial therapy in one case and in swithching therapy in the other.

The use of dolutegravir as monotherapy as a switching strategy in suppressed patients has not been so successful[4,5]. Several studies have shown a high rate of virological failure with the development of resistance mutations to dolutegravir. With this bad experience, dolutegravir monotherapy will not be further evaluated as a potential simplification strategy.

GUIDELINES ON ANTIRETROVIRAL THERAPY: MORE RESTRICTIVE

Guidelines on antiretroviral therapy are widely used. Given the important changes provided by clinical trials and the introduction of new drugs, most guidelines are revised every year or, at most, every two years. Surprisingly, we have frequently seen important differences in the recommendations of different guidelines, despite the fact that the root information is the same throughout the world.

Classically, international or local guidelines could be included in one of two classes: those that recommended a higher variety of first-choice regimens to initiate antiretroviral therapy, and those that limited the number of first choice options. The last edition of most guidelines, however, has converged in being more restrictive, limiting the preferred regimens to those based on integrase inhibitors[6,7]. Protease inhibitor- or non-nucleoside- based regimens have been placed as alternative regimens, with only a few exceptions[8,9]. The high efficacy and good tolerability shown in controlled clinical trials justify the consideration given to the integrase inhibitor class.

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Update on the diagnosis of invasive fungal infection

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ABSTRACT

The number of patients at risk of suffering invasive fungal infection (IFI) is increasing. Because of its high mortality, new rapid and accurate diagnostic tools are needed. Last advances in invasive candidiasis diagnosis comprise Peptide Nucleic Acid Fluorescent In-Situ Hybridization (PNA-FISH), direct MALDI-TOF or multiplex acid nucleic testing. While all of them rely in positive blood cultures, T2Candida® uses PCR coupled with T2Magnetic resonance detection directly in whole blood, allowing detection of 1-3 UFC/mL of *Candida* in about four hours. Beyond galactomannan (GM), novelties in IFI caused by molds include the international standardization of PCR techniques, with several commercial kits available. A combination of GM and PCR appears to be a good diagnostic strategy for invasive aspergillosis. PCR coupled to electrospray ionization/mass spectrometry and detection of volatile organic compounds in exhaled air by gas chromatography/mass spectrometry are other promising approaches to IFI diagnostic that still need to be validated.

Key words: diagnosis, *Candida*, mold.

Actualización en el diagnóstico de la infección fúngica invasora

RESUMEN

El número de pacientes en riesgo de padecer infección fúngica invasora (IFI) está en aumento. Debido a su elevada mortalidad, es necesario disponer de nuevas herramientas diagnósticas más rápidas, sensibles y específicas que las que disponemos en la actualidad. Los últimos avances en el diagnóstico de la candidiasis invasora incluyen Hibridación In Situ de Ácidos Péptidonucleicos (PNA-FISH), MALDI-TOF directo o PCR múltiple. Mientras que todas estas técnicas se realizan sobre frascos de hemocultivo positivos, T2Candida® se basa en una PCR con detección por resonancia magnética T2 directamente en sangre total, y permite la detección de entre 1-3 UFC/mL de *Candida* en aproximadamente 4 horas. Más allá del galactomanano (GM), una de las últimas novedades en el diagnóstico de IFI causada por hongos filamentosos es la estandarización internacional de las técnicas moleculares, con la aparición de varios kits comerciales. Una buena estrategia para el diagnóstico de aspergilosis invasora es la combinación de GM y PCR. La PCR asociada a ionización por electrospray/espectrometría de masas y la detección de compuestos orgánicos volátiles en aire exhalado mediante cromatografía de gases asociada a espectrometría de masas son otras aproximaciones prometedoras al diagnóstico de IFI que aún deben ser validadas.

Palabras clave: diagnóstico, *Candida*, hongo filamentoso.

An increasing number of patients are at risk of suffering opportunistic invasive fungal infection (IFI): solid organ transplant (SOT) recipients, haematological patients undergoing hematopoietic stem cell trans-plantation (HSCT), neoplastic diseases, AIDS, immunosuppressive therapy, major surgery, chronic pulmonary diseases, etc. Among them, invasive candidiasis causes almost 70% of all IFIs around the world, followed by cryptococosis (20%), and aspergillosis (10%)[1]. Other molds such as *Zygomycetes*, *Fusarium* and *Scedosporium* species are emerging in the last few years and represent a cause of concern[2]. The mortality attributed to invasive candidiasis varies from 30-50%, and it can reach almost 100% in some molds[3]. Late initiation of antifungal therapy significantly increases mortality in invasive candidiasis[4], which is why early diagnosis techniques are urgent.

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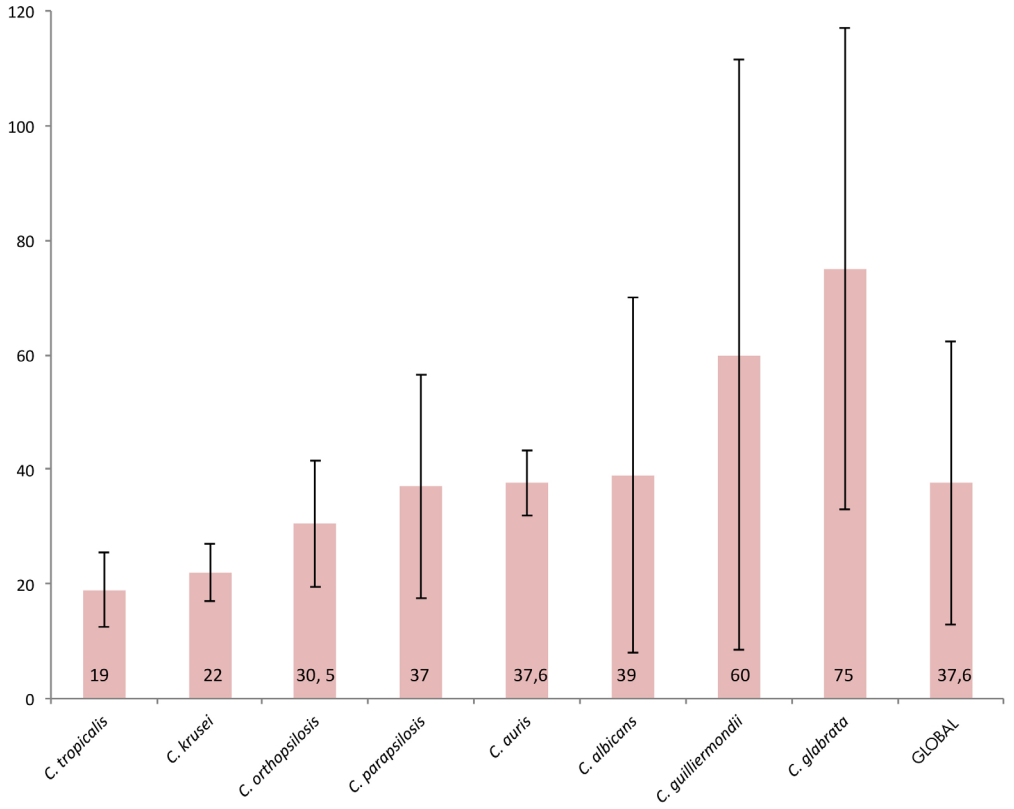

Figure 1 | **Medium time of growth (hours) of different *Candida* species in blood cultures Data from 258 candidemia episodes in intensive care units at La Fe University Hospital**

INVASIVE CANDIASIS

Despite its low sensitivity (50-60%), blood culture remains as the gold standard method to diagnose candidemia. Time to positivization of blood cultures varies between different species of *Candida* from 19-22 hours in *Candida tropicalis* and *Candida krusei* to 60-75 hours in species such as *Candida guillermondii* or *Candida glabrata*, with a mean time of growth of 37.6 hours (data from 258 candidemia episodes at La Fe University Hospital, figure 1). Once the blood culture is positive, it takes about 15 minutes to learn whether the causing agent of the blood stream infection is a yeast with a gram stain. However, final identification with traditional methods such as Auxa*Color*™ 2 (Bio-Rad, Marnes-la-Coquette France), Vitek® 2 YST ID card (bioMérieux, Marcy l'Etoile, France) or CHROMagar™ Candida (CHROMagar, Paris, France) takes around 24-48 hours. Some novel strategies to shorten this diagnostic period include Peptide Nucleic Acid Fluorescent In-situ Hybrydization (PNA-FISH), direct MALDI-TOF from the blood culture bottle, multiplex acid nucleic testing like Filmarray, or non-blood culture based methods such as T2Candida (figure 2):

Yeast Traffic Light PNA FISH™ (AdvanDX; Woburn, MA) is a next-generation, three-probe Peptid Nucleic Acid Fluorescence In-Situ Hybridization system which is FDA cleared for the rapid identification of *C. albicans/C. parapsilosis* (green fluorescence), *C. glabrata/C. krusei* (red fluorescence) *and C. tropicalis* (yellow fluorescence). It is performed from positive blood cultures in 90 minutes. The colour also provides a preliminary indication of fluconazole susceptibility, with green suggesting likely susceptibility, red indicating likely resistance, and yellow suggesting concern for inducible resistance. Other *Candida* spp., non-*Candida* yeast, and bacteria show no fluorescence[5]. The utilization of PNA FISH has demonstrated a reduction in the median time required for identification in *C. albicans* to 9.5 h compared to the standard culture median time of 44 h. The most pronounced effect of the PNA FISH test is on the reduction of echinocandin usage in patients with candidemia due to *C. albicans*. In these patients fluconazole substituted caspofungin after notification of the PNA FISH results, with a significant decrease in antifungals costs of $1,978 per patient[6].

MALDI-TOF technology is available in more hospitals each day. The biggest advantage of this technique is its promptness. It takes no more than 5 minutes to identify a microorganism from isolated colonies. To accelerate even more this process microbiologists have developed a protocol to identify yeasts with MALDI-TOF directly from positive blood culture bottles in 30 minutes without performing a subculture. The proto-

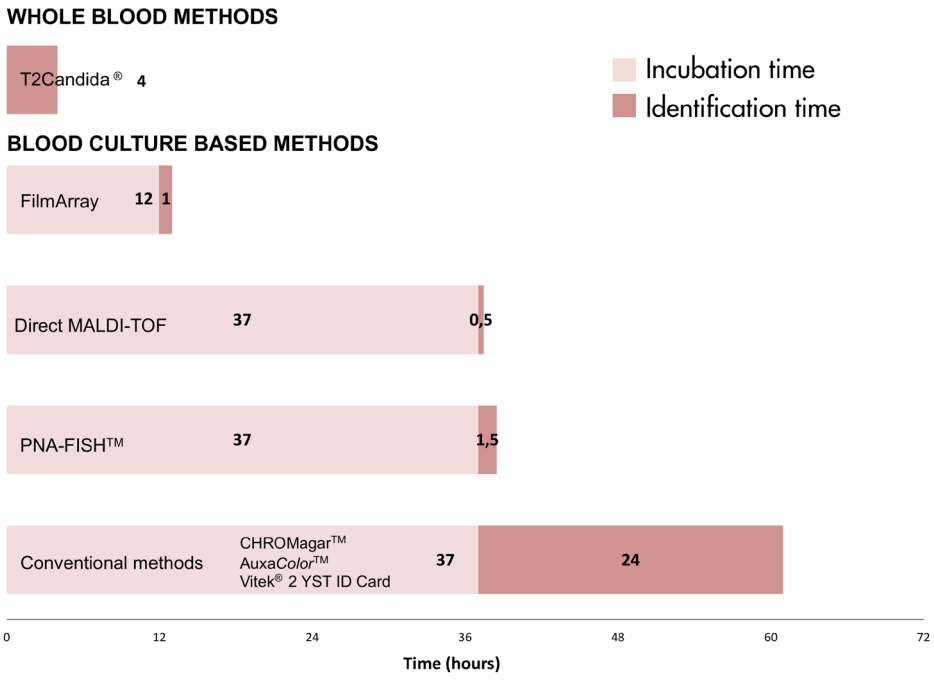

Figure 2 Graphic representation of time (hours) to yeast identification depending on employed technique.

Figure 3 T2Candida® instrument

cols available for the Bruker Biotyper MALDI-TOF MS (Bruker Daltonik GmbH Leipzig, Germany) and for the VITEK® MS (bioMérieux, Marcy l'Etoile, France) systems comprise several centrifugations, washings and treatments with 0.1% Tween 80, ethanol, formic acid and acetonitrile in order to concentrate the sample, precipitate proteins and remove completely

all blood cells that can interfere with the yeast spectra. Results of this protocol make MALDI-TOF one of the more promising alternatives to accelerate species-level identification of yeasts from blood cultures, with a sensitivity of 95.9% for *C. albicans* and 86.5% for non-*albicans Candida* species, being *C. guillermondii* the specie most frequently missed. The main limitation of this process is that it does not identify polifungal infections and that sample preparation requires time and expertise[7].

Other possibilities that are currently being developed and used in clinical settings are **multiplex-PCR platforms**. In this area one of the available tools nowadays is the FilmArray platform (FA; BioFire, Salt Lake City, UT), a closed diagnostic system allowing high-order multiplex PCR analysis with automated readout of results in one hour directly from positive blood cultures or after a 12 hours incubation. The FilmArray BCID panel for blood cultures targets 24 pathogens: eleven Gram-negative bacteria, eight Gram-positive bacteria and three antibiotic resistance genes, as well as five *Candida* species: *C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis*[8]. Filmarray has demonstrated a sensitivity of 99.2% with a 99.9% of specificity for all yeasts and 99.8% specificity for *C. albicans* in a multicentre controlled trial with 2,207 positive blood cultures[9]. The major advantages of this tool are that it covers a wide number of common pathogens with a good sensitivity and specificity, requires very little technical preparation and a very short time: it provides results in one hour with only 5 minutes for assay setup; and it detects polimicrobial infections. However, the fact that only one sample can be run at a time might be a rate-limiting step for a rapid diagnostic method. On the other hand, the emergence of pathogens such as *C. auris* in some hospitals make it necessary to evaluate the usefulness of this multiplex PCR techniques according to local epidemiology.

The main disadvantage of all these three methods of identification is that they still rely on a positive blood culture, which can take from 20 to more than 60 hours. As time in sepsis is gold, a new approach has been developed to shorten the time needed for invasive candidiasis diagnosis: **T2 magnetic resonance (T2MR)** is an assay that can be performed in whole blood without any previous incubation or DNA extraction. It lyses the *Candida* cells, amplifies the DNA with pan-*Candida* PCR primers, and finally detects the amplified product directly in the whole-blood matrix by agglomeration of superparamagnetic nanoparticles bearing target-complementary probes. Nanoparticle clustering yields changes in the T2 relaxation time, making it detectable by magnetic resonance. T2Candida® can detect five *Candida* species (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*) and results in a >10-fold decrease in time to result while achieving detection sensitivities of ~1 colony-forming unit (CFU)/mL. It only needs 2-4 mL of whole blood, reason why it can be used in paediatric patients too. Findings in a 12 hospitals multicentre study, with 1,801 samples, endorse the utilization of T2Candida, with a sensitivity and specificity of 91.1% and 99.4% respectively, a limit of detection ranging from 1-3 CFU/mL depending on the *Candida* specie and a NPV of 99.4% in a 5% prevalence population, with a meantime to negative result of 4.2 hours. The ability to rapidly exclude candidemia can have a significant impact in clinical practice decreasing the number of patients on empiric antifungal therapy and thus the incidence of resistant strains, the potential side effects of antifungal treatment, and a substantial reduction in healthcare costs[10].

T2Candida® has also proved to detect deep-seated invasive candidiasis (IC) with negative blood cultures that were confirmed later by a positive tissue biopsy or by culture of a normally sterile site, in patients who were on antifungal therapy. In some cases, the discovery of the focus was performed even a week later and in one case, 12 sets of blood cultures were negative prior to diagnosis by biopsy. These findings highlight the potential of T2Candida in detecting not only candidemia but also deep-seated candidiasis[11].

An economical model has showed that T2Candida® has the potential to significantly reduce costs and mortality rates in patients at high risk for candidemia. In a hospital admitting 5,100 high-risk patients per year, assuming a 3% prevalence rate, the estimated potential savings per patient with candidemia is $26,887, a 48.8% reduction in hospital costs in candidemia. The application of species-specific therapy enabled by rapid *Candida* identification demonstrated potential savings of over 30 lives per year in a typical hospital setting, corresponding to a 60.6% reduction in mortality. Moreover, the potential savings in empirical therapy in non candidemic patients would be $4,521,081 (42.8%) in total costs or $886 per tested patient[12].

Therefore T2Candida® is a rapid and simple diagnostic tool with a response time of less than 4 hours and sample preparation of less than 10 minutes. It requires a minimum amount of blood allowing pediatric use, has a very low limit of detection (1-3 UFC/mL) and it is capable of detecting IC without candidemia, with the potential to save almost 50% of candidemia related-costs. However, it only detects five species, grouped in four options, the reagents have a very short expiration date and it costs 300 € per sample, cost that has its counterpart in total hospital savings but that needs to be very well justified to the hospital management[10-12].

INVASIVE FILAMENTOUS FUNGAL INFECTIONS

Classical mold IFI diagnosis relies on culture of samples such as sputum or bronchoalveolar lavage (BAL), along with histopathologic detection of the fungus on biopsy specimens. But culture is slow and has a low PPV (around 72%), which can be even lower in non-haematologic patients or those on antifungal therapy[13].

There had been advances in the diagnosis of invasive aspergillosis (IA), the most widespread being **galactomannan** (GM) in serum or BAL. However, GM is far from being a perfect diagnostic tool, its sensitivity and specificity do not exceed 85%, antifungal prophylaxis reduces specificity, and antifungal therapy reduces the sensitivity of the test[13]. Nowadays IFI diagnosis relies on late non-pathognomonic radiologic findings, reason why there is still a need of new diagnostic tools to improve mold IFI diagnosis.

There are multiple **PCR techniques** targeting *Aspergillus* spp. or *A. fumigatus*. The lack of standardization of these systems has prompted an European initiative for standardization of *A. fumigatus* PCR (EAPCRI) which, through the distribution of quality control panels, has leaded to the creation of recommendations for PCR protocols and a standardization of the technique[14]. Although PCR was excluded from EORTC/MSG definitions of IA because of the lack of a standard methodology, it will probably be included in next editions[15]. There are now several commercial assays for *A. fumigatus* PCR: MycoGENIE (Ademtech), AsperGenius (PathoNostics), Fungiplex (Renishaw) and Septifast (Roche). They are validated for blood, bronchoalveolar lavage, and even for biopsies (MycoGENIE). Most commercial assays dispose of a standardized PCR amplification system that when combined with EAPCRI recommendations provide a fully standardized approach[16].

The most interesting advance in PCR techniques is AsperGenius (PathoNostics, Maastricht, the Netherlands), a new multiplex real-time PCR assay consisting of two multiplex real-time PCRs, one that identifies clinically relevant *Aspergillus* species (*A. fumigatus* complex, *A. terreus*, *A. flavus, A. niger, A. nidulans*), and one that detects the TR34, L98H, T289A, and Y121F mutations in CYP51A and differentiates susceptible from resistant *A. fumigatus* strains. Its overall sensitivity, specificity, PPV, and NPV are 84.2%, 91.4%, 76.2%, and 94.6%, respectively[17].

The diagnostic odds ratio for *A. fumigatus* PCR is comparable to that of GM, with a sensitivity of 84-88% in blood and 76.8-79.6% in BAL and a specificity of 75-76% and 93.7-94.5% respectively. Its specificity in BAL is greater than GM's, while in blood is significantly lower. Sensitivity appears higher for PCR in blood than for GM. It looks like combining PCR in blood for screening and PCR in BAL for a diagnostic test is an interesting approach[16].

Moreover, early diagnosis and preemptive therapy of IA with a combination of PCR and GM compared to GM alone has showed a relative risk reduction of 68.1% in proven or probable IA and a reduction in time to diagnosis of one week in a large multicenter randomized trial conducted in 13 Spanish centers. This fact suggests that DNAemia precedes the release of fungal GM into the bloodstream, therefore a strategy combining diagnosis with both PCR and GM looks quite appealing[18].

Both PCR and GM are oriented to the detection of *A. fumigatus*, but the emergence of other filamentous fungus like Mucorales or *Scedosporium* species urge the development of panfungal diagnostic systems[2]. In this area, both PCR amplification followed by Electrospray Ionization/Mass Spectrometry (PCR/ESI-MS) and detection of Volatile Organic Compounds (VOCs) in exhaled air by Gas Chromatography/Mass Spectrometry (GC-MS) are the latest approaches for invasive mold infection diagnosis:

A broad-range multilocus **PCR/ESI-MS** to detect and identify fungal organisms directly from clinical specimens has showed to provide a rapid and sensitive detection and identification of fungal organisms directly from BAL specimens. It even detected and identified at least one fungal organism in 47.3% of the specimens where the standard culture method failed, and shows an agreement in identification with standard procedures of 62.7% at species level and 81.3% at genus level[19]. There is already a commercial platform of PCR/ESI-MS: Iridica™ (Abbott, USA). It detects more than 200 fungal species; performance time is less than six hours and can be run both in whole blood and in BAL, with a cost of only $30 per sample.

On the other hand, there is an increasing interest in the use of biomarkers like **VOCs** in exhaled breath for clinical diagnosis and management of diseases such as asthma, COPD or lung cancer. There is, too, an incipient research in the diagnosis of infectious diseases using these volatile biomarkers. The biggest advantage of exhaled breath is that it is characteristically non-invasive, reason why invasive techniques such as BAL and bronchial biopsy could be avoided[20,21].

2-pentylfuran appears to be a good marker of invasive aspergillosis (IA), with a sensitivity of 77% and a specificity of 78% compared to BAL or sputum culture[22]. However, *A. fumigatus* produces a great variety of characteristic VOCs in vitro, that can vary depending on the environment conditions or antifungal therapy[23,24] . It looks like a set of metabolites, rather than a very specific one, can be the "breath-signature" of each fungus, and it has been proved that 4 metabolites (α-trans-bergamotene, β-trans-bergamotene, β-vatirenene, and trans-geranylacetone) can differentiate patients with and without IA with 94% sensitivity and 93% specificity[24]. Further investigation needs to be carried out in this very interesting and applicable technique.

It should not be forgotten that a traditional technique such as direct microscopic examination of a sample with calcofluor white remains the most economic and rapid diagnostic tool and, although its sensitivity is low, it can detect mold IFI in less than 15 minutes. However, it requires expertise and it is not available in hospitals were there are no clinical microbiologists on call.

Although at the moment there is no perfect diagnostic method for invasive fungal infection, significant advances have been made in the last few years. Timely diagnosis of IFI is necessary to prevent its high morbidity and mortality, reason why further studies standardizing the already developed technologies and deepening in the knowledge of novel tools such as MALDI-TOF, T2Candida®, PCR/ESI-MS or VOCs detection with GC-MS are needed.

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Invasive candidiasis in the neutropenic patient

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ABSTRACT

There are major differences in the epidemiology and prognosis of invasive candidiasis and candidemia in the neutropenic patient; however, a recent study performed in Spanish hospitals (Candipop) confirmed that mortality at 1 month is 30%, which is similar to that observed in the general population. Although *Candida albicans* is the most frequently isolated species, *C. tropicalis*, *C. glabrata*, and *C. krusei* are more prevalent than in non-neutropenic patients. The benefit of neutrophil transfusion is unclear, and catheter withdrawal must be tailored and based on confirmation of the diagnosis. Echinocandins are the first-line option for therapy and have a better safety profile than other agents.

Candidasis invasiva en el paciente neutropénico

RESUMEN

Existen diferencias significativas en la epidemiología y pronóstico de la candidemia y candidiasis invasiva en el paciente neutropénico, aunque una similar mortalidad a la observada en la población general (30% al mes) ha sido notificada en un reciente estudio nacional (Candipop). *Candida albicans* es la especie más frecuente pero *C. tropicalis*, *C. glabrata* y *C. krusei* tienen una mayor prevalencia que en los pacientes no neutropénicos. No está claro el beneficio de la transfusión de neutrófilos y la retirada de catéter debe ser individualizada. Las equinocandinas suponen el tratamiento de elección dada su eficacia y perfil de toxicidad en relación a otros antifúngicos.

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EPIDEMIOLOGY

The Candipop study, which recently analysed 752 episodes of candidemia in 29 Spanish hospitals between April 2010 and March 2011, confirmed that mortality was 30% during the first 30 days and 13% during the first week after diagnosis. The independent factors associated with mortality during the first 7 days were age, primary origin of candidemia, presence of septic shock, and administration of the appropriate antifungal drug. Withdrawal of the catheter did not reduce mortality overall, although early withdrawal did (first 48 hours)[1].

In patients with oncologic-hematologic conditions, the factors associated with mortality were similar to those of the general population. However, compared with patients with solid tumours, patients with hematologic neoplasms had a significantly higher incidence of neutropenia and mucositis and a lower frequency of catheter-associated candidemia and required the catheter to be withdrawn less often[2]. This less relevant role of the catheter as the origin of candidemia in patients with haematological disease has also been confirmed elsewhere[3].

The species causing candidemia also differs in patient with hematologic conditions. As in the general population, *Candida albicans* and *C. parapsilosis* are the most common species, although endogenous species (*C. tropicalis*, *C. glabrata*, and *C. krusei*) are much more prevalent than in the general population[4]. The greater mortality caused by these three species has been confirmed in many studies, some of which established an association with greater virulence or greater resistance to azoles. However, it is not easy to separate this higher species-dependent mortality from host-dependent mortality. The above mentioned species are more frequent in patients with profound and severe neutropenia, which, together with a high APACHE score, are the factors most significantly associated with mortality in many candidemia series[5,6].

RECOMMENDATIONS ON TREATMENT OF INVASIVE CANDIDIASIS AND CANDIDEMIA IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISORDERS

Several clinical guidelines and national and international consensus statements have been published in recent years[7-12].

In 2012, ESCMID published specific guidelines on the management of candidemia in patients with hematologic cancer who had undergone bone marrow transplantation[9]. The guidelines do not recommend prophylaxis for post-chemotherapy neutropenia or in autologous transplantation. However, they do justify prophylaxis in allogenic transplantation in the following situations: neutropenia (recommendation grade AI for fluconazole, posaconazole, voriconazole, and micafungin), during the first 100 days in the absence of graft-versus-host disease (GVHD) (recommendation grade AI for fluconazole and posaconazole) and in the presence of GVHD (recommendation AI for fluconazole and posaconazole). In the case of empiric treatment for patients with long-term neutropenia, their highest recommendation is caspofungin (AII_t) and micafungin (AII_t), followed by liposomal amphotericin B (BII_t), fluconazole (CII_t), voriconazole (CII_t), and posaconazole (DII_t). For targeted treatment, the guidelines suggest caspofungin (AI) or liposomal amphotericin B (AI) and recommend catheter withdrawal (AII_u). Lastly, transfusion of granulocytes is considered a last resort in some cases of candidemia/candidiasis in neutropenic patients (CIII).

In 2016, the Infectious Diseases Society of America (IDSA) re-edited its guidelines on candidemia in the general population and for different conditions, including neutropenia[12]. Table 1 summarizes the main recommendations. Of particular interest is the recommendation of echinocandins as initial therapy and stepping down to fluconazole after recovery from neutropenia in clinically stable patients infected by a sensitive strain. The recommendations give more weight to transfusion of granulocytes, although the recommendation is weak and the level of evidence low; however, withdrawal of the catheter is recommended on an individual basis (strong recommendation, low level evidence).

ROLE OF WITHDRAWAL OF INTRAVENOUS CATHETER IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISEASES AND CANDIDEMIA

Various studies have confirmed that systematic early withdrawal of vascular catheters in patients with candidemia reduces mortality[13-16], and this recommendation is included in most guidelines[7-12].

However, systematic withdrawal of vascular catheters has been criticized in patients with candidemia. Nucci et al analysed the impact of catheter withdrawal in two multicentre studies[17]: a 2-armed study comparing micafungin and liposomal amphotericin B[18] and a 3-arm study comparing 2 doses of micafungin (100 mg/d and 150 mg/d) with caspofungin 50 mg/d[19]. The catheter was removed during the first 48 hours in 354 of 842 evaluable patients and after 48 hours in 180 patients; it was left in place in 308 patients. The univariate analysis showed this approach to be successful and survival at 28 and 42 days to be higher in cases where the catheter was left in place. However, catheter removal did not affect control of recurrent candidemia or microbiological eradication. Finally, the multivariate analysis did not confirm an independent association between catheter withdrawal and success of therapy or survival at 28 or at 42 days. Only neutropenia, a high APACHE score, and advanced age were significant.

The apparent discrepancy between the results of this study and other similar studies lies in the differences in prevalence of the intravenous catheter as the source of candidemia. Studies in which the intravascular catheter is the main source of candidemia in >40% of cases (eg, on medical wards or in intensive care units) show that controlling the site of infection by withdrawing the catheter provides clear benefits. However, in situations where the

Table 1 **Recommendations on treatment of candidemia in neutropenic patients (adapted from reference 12; IDSA 2016 guidelines, GRADE protocol)**

		Recommendation	Evidence
1	Echinocandins: initial treatment	Strong	Moderate
2	Lipid amphotericin B: alternative (greater toxicity)	Strong	Moderate
3	Fluconazole: alternative (no previous azole therapy, noncritical patient)	Weak	Low
4	Fluconazole/voriconazole: step down (if sensitive strain, no neutropenia, control of candidemia, noncritical patient)	Weak	Low
5	Voriconazole: alternative (if also necessary to cover filamentous fungi)	Weak	Low
6	If *Candida krusei*: echinocandins, lipid amphotericin B, or voriconazole	Strong	Low
7	Duration of treatment: 2 weeks (if candidemia is controlled, no distant foci, clinical improvement)	Strong	Low
8	Ophthalmological examination after resolution of neutropenia	Strong	Low
9	Withdrawal of venous catheter on an individual basis	Strong	Low
10	Granulocyte transfusion: if persistent candidemia and neutropenia	Weak	Low

origin of candidemia may be endogenous and not vascular, such as in the neutropenic patient or in patients admitted to surgical wards, prevalence is lower, and recommendations on catheter withdrawal should be tailored after application of diagnostic techniques, including differential blood cultures.

NEUTROPHIL TRANSFUSION

Three single-centre retrospective studies have highlighted the key role of neutrophil transfusion in control of candidemia in the neutropenic patient[20-22]. A similar protocol was applied in all three studies, namely, donors received granulocyte colony-stimulating factor (600 µg), dexamethasone (8 mg), and a high number of transfusions (>8 per patient) with a high neutrophil count (>50 x 10^9). All 3 studies reported control of candidemia in >50% of cases and a frequency of adverse effects <10% with respect to the low baseline percentage of cross-matching and anti-polymorphonuclear antibodies.

The only multicentre randomized trial to evaluate the role of granulocyte transfusion in neutropenic patients with candidemia was performed with 74 adult patients in Germany[23]. Dexamethasone was not used, and the richness of the polymorphonuclear cells in the units transfused and the frequency of transfusion were lower than in previous studies. The study did not establish significant differences in control of candidemia, and survival at 28 days was similar to that of the control group (82% vs. 84%). In addition to these limitations, the authors also report major limitations (eg, low-risk population, delay between randomization and transfusion), which made it difficult to reach robust conclusions, and agree that new studies are necessary.

KEY ROLE OF ECHINOCANDINS IN THE TREATMENT OF CANDIDEMIA IN THE NEUTROPENIC PATIENT

A recent meta-analysis of 1,915 patients with candidemia confirmed that treatment with echinocandins was an independent factor associated with low mortality (OR, 0.65; 95%CI, 0.45-0.94), as was catheter withdrawal (OR, 0.50; 95%CI, 0.35-0.72)[24].

Most clinical trials on administration of fluconazole to treat candidemia carried out some years ago excluded neutropenic patients, and no controlled clinical trials with lipid amphotericin were performed before the advent of the echinocandins.

In the study by Mora et al (caspofungin vs conventional amphotericin to treat candidemia), 13% and 9% of patients, respectively, were neutropenic, and the response in this subgroup was 50% and 40%, which was slightly lower than that observed in the overall population (73% and 62%, respectively[25].

Kuse et al (micafungin vs liposomal amphotericin in candidemia) also included a significant number of neutropenic patients (12% and 8%, respectively) and confirmed a response of 75% and 80%, which was similar to that obtained in the overall population[18].

Papas et al (micafungin 100 mg/d vs micafungin 150 mg/d vs caspofungin 50 mg/d in patients with candidemia) found that 11%, 9%, and 6% of patients were neutropenic, with a response of 82%, 53%, and 64%, respectively[19].

Reboli et al (anidulafungin vs fluconazole for treatment of candidemia) found that the number of neutropenic patients in both arms was ≤3%, thus precluding evaluation of the role of anidulafungin in this type of patient[26].

Finally, Walsh et al found a 67% response to caspofungin (vs 50% for liposomal amphotericin B) in neutropenic patients with confirmed candidemia and fever receiving empirical treatment[27].

A recent meta-analysis including various of the studies mentioned above specifically analysed the key role of echinocandins in patients with neutropenia[28] and revealed a nonsignificant difference in favour of treatment with echinocandins (OR, 0.73; 95%CI, 0.42-1.29), with a clearly beneficial safety profile.

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Comments on practice guidelines for the diagnosis and management of aspergillosis made by the IDSA in 2016

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ABSTRACT

We sought to review the most important updates in the treatment of aspergillosis after the publication of the clinical practice guidelines for the diagnosis and management of invasive aspergillosis (IA) by the Infectious Diseases Society of America. Our aim is to discuss some of the key aspects concerning the following topics: early initiation of antifungal therapy, antifungal agent of choice, follow-up of patients with IA, and breakthrough aspergillosis.

Comentarios sobre las guías IDSA 2016 de diagnóstico y tratamiento de la aspergilosis

RESUMEN

Tras la publicación de la nueva guía de práctica clínica sobre el diagnóstico y manejo de la aspergilosis invasora (AI) de la Infectious Diseases Society of America, se ha realizado una revisión de los puntos más importantes de la actualización del tratamiento de la aspergilosis. Por dicho motivo, a continuación se discutirán los siguientes aspectos claves de interés: tratamiento precoz, tratamiento antifúngico de elección, seguimiento de los pacientes con AI y aspergilosis de brecha.

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INTRODUCTION

Previous clinical practice guidelines for the diagnosis and management of invasive aspergillosis (IA) published in 2008 by the Infectious Diseases Society of America (IDSA) were updated in 2016[1]. In this context, we hereby review the most important novelties in the treatment of aspergillosis. Our aim is to discuss some of the key aspects concerning the following topics: early initiation of antifungal therapy, recommended antifungal agent, follow-up of patients with IA, and management of breakthrough aspergillosis.

EARLY INITIATION OF ANTIFUNGAL THERAPY

Two of the essential tools to successfully manage these infections are to know the physiopathogenesis of the filamentous fungi, and to identify the host immune response to the aggression.

The spores participate in the earliest stage of the aspergillus pathogenesis. After being inhaled by the host, the spores are recognised as foreign and are subsequently destroyed by the immune system. However, in some hosts spores find it easier to reach the lower respiratory tract, where they are deposited in the alveoli. In the neutropenic host, spores turn into hyphae very easily, thus creating an angioinvasive aspergillosis. In other states of immunosuppression, such as patients with graft-versus-host disease and corticosteroid therapy, some spores turn into hyphae while others cause important polymorphonuclear granulocytes (PMN) recruitment and tissue damage[2].

For all these reasons, the length of time between inhalation of spores and the manifestations of the disease may vary largely. A recent paper describes a noticeable increase in the diagnosis of IA 28-42 days after a considerable build-up of ambient spores in the city of Barcelona[3]. In this context, the diagnosis of early forms of aspergillosis remains a challenge.

Recent investigations have revealed that the halo sign observed in the chest CT is an early sign of the infection. This radiologic image shows a macronodule (≥ 1 cm in diameter) surrounded by a perimeter of ground-glass opacity, without histopathological evidence of necrosis. Greene et al[4], documented that patients who start antifungal treatment on the basis of the identification of a halo sign by chest CT show a significantly better response to treatment and improved survival than those who initiate treatment after observing air crescent signs (suggestive of necrosis and characteristic of later-stage disease) in radiological assessments.

The latest guidelines recommend early initiation of antifungal therapy in patients with strongly suspected IA. In fact, they recommend that treatment should be warranted while a diagnostic evaluation is conducted.

RECOMMENDED ANTIFUNGAL REGIMEN

2016 IDSA guidelines establish voriconazole as the antifungal choice for IA treatment. This recommendation is mainly based on Herbercht's research and his comparison study between voriconazole and amphotericin B deoxycholate[5]. This study showed successful outcomes in 52.8% of the patients in the voriconazole group (complete responses in 20.8% and partial responses in 31.9%) and 31.6% of those in the amphotericin B group; and the survival rate at 12 weeks was also higher in patients treated with voriconazole (70.8 vs. 57.9; hazard ratio, 0.59; 95% confidence interval, 0.40-0.88). Other observational studies also support that voriconazole treatment is associated with better outcomes in patients with IA[6-9].

Voriconazole metabolism is highly variable between subjects. 2016 IDSA guidelines recommend and confirm the importance of therapeutic drug monitoring (TDM) when voriconazole, both po and iv, is used. A randomized controlled trial with 110 patients who were administered voriconazole for 12 weeks, revealed that patients submitted to routine TDM improved their treatment response in invasive fungal infections (IFI) (81% vs. 57%, p=0.04) and reduced drug discontinuations due to adverse events (4% vs. 17%, p=0.02)[10]. The first levels of voriconazole should be measured between days 5 and 7, when the most stable levels are most probably attained. The therapeutic aim is to reach levels between 1.5 and 5 mg/L. It is still unclear how voriconazole doses could be modified if monitored values prove to be too high or too low. The European Conference on Infections in Leukaemia (ECIL) published a guiding algorithm in December 2015 establishing patterns to be followed depending on administration method, usual dose, and blood levels of the antifungal drugs, which could be used as a valuable resource[11].

An important new aspect of these guidelines, is the positioning of isavuconazole as a treatment choice for IA with identical level of evidence as voriconazole. Maertens et al carried out a phase 3, randomised-controlled, non-inferiority trial with 527 patients to compare the use of isavuconazole vs. voriconazole for the primary treatment of invasive mold disease, and proved the non-inferiority of isavuconazole in terms of clinical efficiency[12]. Mortality from first dose of study drug to day 84 was similar between treatment groups in both intention to treat populations (treatment difference -1.1%, 95% CI -8.9-6.7). The proportion of patients with serious treatment-emergent adverse events was similar between both groups. However, significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (109 [42%] vs. 155 [60%]; p<0.001), especially hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole (21 [8%] vs. 35 [14%]).

Another important topic is the positioning of a combined antifungal therapy with voriconazole and an echinocandin as a first-line option in selected patients with documented IA. Marr et al compared the administration of voriconazole-anidulafungin with voriconazole-placebo, in a randomized trial of 454 patients with haematologic malignancies and haematopoietic cell transplantation[13]. Mortality rates at week 6 were 19.3% for combination therapy and 27.5% for monotherapy (difference, -8.2 percentage points [95% CI -19.0-1.5]; p=0.087). In the subgroup of patients diagnosed of probable IA that was based on radiographic abnormalities and galactomannan antigen positivity in serum or BAL, the results were similar: mortality after 6 weeks was lower in combination therapy than monotherapy (15.7 vs. 27.3; p=0.037). This study was the first to use initial voriconazole doses of 300 mg/12h in a clinical setting. Compared with previous studies that had used 200 mg/12h, no increase in toxicity was documented.

In situations in which hepatic toxicities or drug interactions warrant non-azole alternatives, and when voriconazole-resistant molds remain of concern, the recommendation is to use liposomal amphotericin B (AmB). In highly immunocompromised patients, the effectiveness of AmB 3 mg/kg/day as first-line therapy for IA is demonstrated, with a response rate of 50% and a 12-week survival rate of 72%[14].

With regard to the duration of treatment, it is difficult to make recommendations. It depends on three key factors: the host, the clinical and microbiological response, and the evolution of CT findings.

FOLLOW-UP OF PATIENTS WITH INVASIVE ASPERGILLOSIS

The follow-up of invasive aspergillosis patients is difficult, as they are usually complex patients with abundant intercurrent processes. Patient's assessment is based on clinical evolution, performance of CT examinations, and monitoring of microbiological tests.

Repetition of a CT scan before 2 weeks after the start of treatment is not usually recommended, due to the paradoxical reaction that can sometimes be observed on the first 14 days

(a radiological worsening that does not necessarily mean a clinical deterioration of the patient).

With regard to microbiological tests, the key biomarker is galactomannan. Miceli et al[15], proved that the evolution of this biomarker over time is a good prognostic index. The correlation between the quantitative serum galactomannan index (within ≤1 week before outcome) and define outcomes was excellent, with k correlation coefficient of 0.87 (95% CI, 0.81-0.93; p<0.001) and 0.91 (95% CI, 0.86-0.96; p<0.001) for survival and global outcome, respectively.

WHAT THERAPEUTIC ACTIONS SHOULD BE TAKEN TO TREAT BREAKTHROUGH ASPERGILLOSIS?

Breakthrough IFI (bIFI) is defined as the IFI suffered by patients undergoing antifungal treatment, which appears 3-5 days after the initiation of such treatment, with prophylactic or therapeutic purpose.

As soon as a bIFI is suspected, examinations should be aimed at determining whether this bIFI is associated to a failure of previous antifungal therapy, to the host immunity, or to the presence of resistant fungi. On the basis of this concept, the guidelines recommend 4 actions: i) if the antifungal prophylaxis is with either voriconazole or posaconazole, pharmacological levels should be monitored; ii) to carry out a CT and a fibrobronchoscopy in order to rule out the presence of resistant fungi; iii) to change the antifungal agent family throughout the rest of the diagnostic process; iv) to reduce immunosuppression to the extent possible.

If TDM certificate low azole levels, bIFI will be probably related to prophylactic failure and adjusting the antifungal levels would arise as an appropriate strategy. Conversely, if TDM shows optimal drug levels, we should look at the possible presence of a resistant fungus, namely *Aspergillus* sp. or other filamentous fungi.

A recent study carried out by Biehl et al[16], compared the response presented by possible, probable, and proven bIFI cases in patients with acute myeloid leukaemia (AML) and allogeneic haematopoietic stem cell transplantation (HSCT). In this study, 250 AML patients with 329 hospitalizations and 409 HSCT patients with 496 hospitalizations were identified. In AML patients, there were 16 (6.4%) proven or probable bIFIs and 44 (17.6%) possible bIFIs. In HSCT patients, there were 14 (3.4%) proven or probable bIFIs and 37 (9.0%) possible bIFIs. A high variety of treatment approaches were observed. Switch from prophylaxis to liposomal amphotericin B was the most frequent approach in AML patients. Overall survival in this population did not differ between patients with or without bIFI (63.3% versus 70.0%; p=0.297). Conversely, the most frequent approach in HSCT patients was to keep the ongoing prophylaxis regimen. In this population, those patients with bIFI presented greater mortality than those patients without suspected infection (49.0% versus 66.8%; p=0.012).

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Empirical treatment of adults with hospital-acquired pneumonia: lights and shadows of the 2016 Clinical Practice ATS/IDSA Guidelines

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ABSTRACT

Hospital-acquired pneumonia (HAP) is a common cause of nosocomial infection associated with significant morbidity and mortality. New clinical practice guidelines for the management of adults with hospital-acquired pneumonia have been published in 2016 by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). This review focuses on the recent recommendations and their limitations. We also focus on new therapeutic options that might improve the treatment and outcomes of these patients.

Tratamiento empírico de la neumonía nosocomial en adultos: luces y sombras de las guías de práctica clínica de la ATS/IDSA de 2016

RESUMEN

La neumonía nosocomial es una causa frecuente de infección intrahospitalaria y tiene una elevada morbilidad y mortalidad. En el año 2016 se ha publicado una nueva guía de práctica clínica para el manejo de la neumonía nosocomial en adultos, elaborada por la Infectious Diseases Society of America (IDSA) y la American Thoracic Society (ATS). Esta revisión comenta nuestra opinión sobre las nuevas recomendaciones y sus limitaciones, así como en las nuevas opciones terapéuticas disponibles que podrían mejorar el tratamiento y pronóstico de estos pacientes.

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Hospital acquired pneumonia (HAP) is defined as an inflammatory process in lung tissue caused by infectious pathogens that is not present at the time of hospital admission and occurring 48 hours or more post admission[1].

It represents the second most prevalent hospital-acquired infection[2], and is an important concern for national public health system due to its high morbidity and mortality as well as the huge amount of health resources that consumes. It is important to note the differences between HAP and ventilator-associated pneumonia (VAP). VAP is defined as the pneumonia that arises more than 48 to 72 hours after endotracheal intubation. Despite this infection is also a nosocomial pneumonia, in the next lines we will refer to HAP exclusively in patients without intubation.

There are different challenges for physicians in the treatment of HAP. There is very little current information regarding the aetiology of HAP. Most data concerning the aetiology of nosocomial pneumonia refer especially to VAP population. A recent review published by our group describes that up to 60% of the cases of HAP are caused by gram-negative bacilli. *Pseudomonas aeruginosa* (24%) and *Klebsiella* spp. (11%) were the most frequently microorganisms isolated. The most frequent gram-positive pathogen associated with HAP was *Staphylococcus aureus*, accounting for 30% of the cases[1]. Remarkably, the risk factors for multidrug resistant HAP are not well defined. Antibiotic resistance is a global health problem worldwide, especially in those infections caused by gram-negative bacilli. The infections caused by these multidrug resistant strains receive often inappropriate antimicrobial therapy and it might negatively impact on outcomes.

New clinical practice guidelines for the management of adults with hospital-acquired pneumonia have been published in 2016 by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS)[3]. In these guidelines, the distinction between "early onset" pneumonia (occurs in the first 96 hours of hospital admission) and "late onset" pneumonia

(appears after >96 hours) has been removed. This division was based on the fact that within the first days of hospital admission, gram-positive cocci still predominate on the flora of the respiratory system. After 5-7 days of illness, oropharynx fibronectin disappears and some receptors that allow the gram-negative rods colonization are exposed. Antibiotic pressure selects multiresistant strains and *P. aeruginosa* colonization[4]. Recent studies have questioned the relationship between the timing of nosocomial pneumonia and the risk of multidrug-resistant (MDR) pathogens. However, most of these researches were focused on VAP[5,6].

The 2016 guidelines on HAP[3] remark two factors to decide the empirical antibiotic therapy for patients with HAP: risk of MDR infection and severity of disease. After the review of several articles, the authors identify the use of prior intravenous antibiotic treatment within 90 days as the only risk factor for MDR HAP. Other factors such as the existence of comorbidity, recent hospital admission, the use of prior oral antibiotics, current hospitalization in an area of high prevalence of multi-drug resistances or previous colonization by multi-drug resistant microorganisms were not taken into account. Those patients who require mechanical ventilation or present shock at the time of diagnosis were categorized as patients who had high risk of mortality. Some measures such as empirical double

Table 1 **Recommended initial empiric antibiotic therapy for hospital-acquired pneumonia (non-ventilator-associated pneumonia) (adapted from reference 3)**

Not at high risk of mortality and no factors increasing the likelihood of MRSA	Not at high risk of mortality but with factors increasing the likelihood of MRSA	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacilin-tazobactam 4.5 g IV q6h	Piperacilin-tazobactam 4.5 g IV q6h	Piperacilin-tazobactam 4.5 g IV q6h
OR	OR	OR
Cefepime 2 g IV q8h	Cefepime or ceftazidime 2 g IV q8h	Cefepime or ceftazidime 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem 500 mg IV q6h	Imipenem 500 mg IV q6h	Imipenem 500 mg IV q6h
Meropenem 1 g IV q8h	Meropenem 1 g IV q8h	Meropenem 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15-20 mg/kg IV daily
		Gentamicin 5-7 mg/kg IV daily
		Tobramycin 5-7 mg/kg IV daily
		OR
		Aztreonam 2 g IV q8h
	Plus:	Plus:
	Vancomycin 15 mg/kg IV q8-12h with goal to target 15-20 mg/mL trough level (consider a loading dose of 25-30 mg/kg x 1 for severe illness	Vancomycin 15 mg/kg IV q8-12h with goal to target 15-20 mg/mL trough level (consider a loading dose of 25-30 mg/kg x 1 for severe illness
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA.
		Options include:
		Piperacilin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacilin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.

If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam-based antibiotic, include coverage for MSSA.

coverage treatment for gram-negative bacilli are recommended only for these patients.

Empirical antibiotic treatments recommended by new guidelines for the different patient subgroups with HAP are shown in the table 1.

We have some concerns about these recommendations. Firstly, some of the empirical antibiotic treatments proposed are not optimal to treat aspiration pneumonia. We would like to point out that this aetiology is important to consider in older patients, in those with cerebrovascular diseases and/or impaired consciousness at presentation and/or in those patients with swallowing difficulties. Secondly, we think that an initial empirical treatment with levofloxacin o ciprofloxacin as a unique therapy to treat gram-negative bacilli might be inappropriate in most countries due to the high prevalence of resistant strains to these drugs[7]. It is also important to point out that not all drugs combinations used for gram-negative bacilli are synergistic and/or appropriate. Thirdly, the empirical use of vancomycin might be severely compromised, given the profile of patients who are currently admitted to the hospital (elderly and with high comorbidity) because of its toxicity. This fact is particularly relevant for patients receiving concomitant treatment with aminoglycosides.

Finally, the 2016 guidelines on HAP suggest that antibiotic therapy should be adjusted according to the results of antibiogram. However, we would like to emphasize that not all antibiotics have the same bactericidal power, side effects and ability of generating resistances. All these factors should be taken into account when definitive treatment is selected.

Five new antibiotics have been approved recently. They are not included in the new guidelines and may be useful in patients with HAP. Ceftolozane-tazobactam is a beta-lactam antibiotic with a similar chemical structure to ceftazidime. Ceftolozane is larger than ceftazidime, so it cannot be removed by efflux pumps. This antibiotic has also full activity against OprD mutant strains. Moreover, the addition of tazobactam provides activity to many class A beta-lactamases. For all these reasons, ceftolozane-tazobactam offers an excellent coverage against *P. aeruginosa*, even for the multi-drug resistant strains. In a total of 2,968 isolates of *P. aeruginosa* consecutively collected from patients hospitalized with pneumonia in 59 medical centres in the USA and 15 European countries, ceftolozane-tazobactam demonstrated a greater *in vitro* activity than currently available cephalosporins, carbapenems and piperacillin-tazobactam[8].

Avibactam is a new beta-lactamases inhibitor, molecularly very different from existing ones. This inhibitor has an intrinsic antibacterial action and a peculiar structure that protects it from hydrolyzation by several beta-lactamases. Ceftazidime-avibactam is a novel cephalosporin/beta-lactamase inhibitor that inhibits the activities of ambler class A and C beta-lactamases and some ambler class D enzymes. This drug offers coverage for most carbapenemase producing-Enterobacteriaceae in Spain.

Ceftaroline is a new cephalosporin that has a great action against gram-positive pathogens. It binds to different PBP, including PBP2a, making it active against methicillin-resistant *S. aureus* (MRSA). It is one of the antibiotics with greater bactericidal effect against gram-positive and has an inmunomodulatory activity by inhibiting some toxins. As most beta-lactams, it does not have major side effects.

Tedizolid is an oxazolidinone with a long half-life and few significant side effects. A double-blind randomized clinical trial is currently underway to compare tedizolid versus linezolid in patients with HAP[9].

Finally, dalbavancin is a recently approved glycopeptide used to treat infections caused by *S. aureus* and MRSA. Its main advantage is its dosage (once a week) and its few side effects[10]. Further information is needed to recommend this drug in patients with HAP.

In conclusion, HAP is a serious and difficult to treat illness. Some new therapeutic options that might improve the treatment and prognosis of patients who develop this infection have recently appeared. Further studies are needed to define high risk patients for MDR-HAP and to check if new antibiotics have any impact to improve outcomes.

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Antimicrobial management in nosocomial peritonitis: microbiota, drug and time

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ABSTRACT

Complicated intra-abdominal infection requires surgical treatment and broad-spectrum empiric antibiotic treatment used early. The rapid spread of multidrug-resistant bacteria has become a serious threat, especially in critical care units. The excessive use of carbapenems has led to carbapenemase-producing Enterobacteriaceae, leaving tigecycline and colistin as therapeutical options. The new antimicrobials, ceftazidime-avibactam and ceftolozane-tazobactam open new horizons in the treatment of multi-drug resistant Enterobacteriaceae. *Candida* peritonitis causes a high mortality in the critical patient. Diagnosis and early treatment are associated with a better prognosis, the administration of an echinocandin being of choice in these patients.

Manejo antimicrobiano en peritonitis nosocomial: microbiota, fármaco y tiempo

RESUMEN

La infección intraabdominal complicada requiere tratamiento quirúrgico y tratamiento antibiótico empírico de amplio espectro utilizado de forma precoz. La rápida diseminación de las bacterias multirresistentes se ha convertido en una grave amenaza en las unidades de cuidados críticos. La excesiva utilización de carbapenémicos ha condicionado la aparición de enterobacterias productoras de carbapenemasas, dejando como opciones terapéuticas a tigeciclina y colistina. Los nuevos antimicrobianos, ceftazidima-avibactam y ceftolozano-tazobactam, abren nuevos horizontes en el tratamiento de enterobacterias multirresistentes. La peritonitis candidiásica condiciona una elevada mortalidad en el paciente crítico. El diagnóstico y el tratamiento precoz están asociados con un mejor pronóstico, siendo de elección en estos pacientes la administración de una equinocandina.

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Intra-abdominal infection (IAI) is a challenge in clinical practice. It is the main cause of postoperative morbidity after abdominal surgery and the most frequent cause of admission into post-surgical critical care units. We understand nosocomial IAI to be an infectious process that occurs over 48 hours after hospital admission, and includes anastomotic leakage, perforation, and abscesses arising as complications of surgery. However, it is estimated that approximately 80% of all intra-abdominal infections are community acquired[1]. More than 21% of nosocomial infections are caused by resistant pathogens[2]. As a consequence, these multi-drug resistant bacteria, which frequently cause intra-abdominal infections, prolong hospital stay (from 6.4 to 12.7 days), increase the number of complications and decrease the efficacy of treatments[3].

In this context, intra-abdominal infection associated with healthcare must also be defined. This term is used to describe infections in those patients who regularly use the healthcare system because of underlying conditions (patients who have had recent hospital admissions, are living in care homes, attending day hospitals, those who have previously taken antibiotics, or are receiving haemodialysis). This definition implies that patients will need initial treatment with broader-spectrum antibiotics than patients with community-acquired infections, due to the presence of microorganisms with a higher degree of resistance to antibiotics.

The so-called core or essential microorganisms of IAIs are Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*) and *Bacteroides* spp. (mainly *B. fragilis*), which should always be covered by empiric antibiotic treatment.

Most of the morbimortality produced by multi-drug resistant bacteria is caused by Gram-negative bacteria, which

account for 27% of the most common pathogens in US hospitals[4]. Enterobacteriaceae in particular are primarily responsible for digestive tract infections.

Based on the most recent data from the European antibiotic surveillance reports, the prevalence of resistance to ESBL-type (beta-lactamase-producing enzymes) *E. coli* and *Klebsiella* varies markedly from one country to another. This is probably related to factors such as the availability of drugs, as well as their restriction, waste, water management and general living conditions. In Spain, there has been a notable increase in the prevalence of ESBL-producing Enterobacteriaceae, from 0.5% in 2000 to 4.04% in 2006. In the data obtained from a Study for Monitoring Antimicrobial Resistance Trends (SMART), in which samples including peritoneal fluid, abscesses and bile were collected, the most frequently isolated organism was *E. coli* of nosocomial origin (49.9%). Of the total of Enterobacteriaceae isolated in IAIs, 7.5% were ESBL producers, most frequently *E. coli* (8.7%), followed by *K. pneumoniae* (8.4%), *Klebsiella oxytoca* (4%) and *Proteus mirabilis* (1.6%). In all ESBL-producing microorganisms, the frequency of these enzymes was markedly higher in nosocomial-acquired than in out-of-hospital acquired infections. There was also an increase in isolates with ESBL parallel to that of the patients' age, reaching a frequency higher than 6% in those over 60 years old[5]. Among the risk factors most frequently identified for the appearance of these Enterobacteriaceae capable of expressing ESBL is previous antibiotic treatment. In this regard, rapid enteric colonisation by bacteria resistant to the antibiotic received has been observed in patients receiving third-generation cephalosporins or piperacillin-tazobactam.

The main species of *Enterococcus* spp. participating in the IAI are *Enterococcus feacalis* (80%) and to a lesser extent, *Enterococcus faecium*. They have a natural resistance to many antibiotics, can be selected and proliferate in weakened patients or recipients of a solid organ transplant. In a previous study of secondary peritonitis, the isolation of a high inoculum of this microorganism was associated with nosocomial origin, a higher score in the Charlson Index and APACHE II, or with a poor outcome[6]. Its presence is also very common in tertiary peritonitis.

Pseudomonas aeruginosa has a greater impact on patients with low responsiveness or those who have undergone invasive treatment such as peritoneal dialysis in the form of primary peritonitis. Among the most relevant risk factors for *P. aeruginosa* bacteraemia, nosocomial acquisition, history of invasive procedures in the preceding 72 hours, immunosuppression, neutropenia and hospital stay > 30 days were identified. Another risk factor for *P. aeruginosa* colonisation/infection in critical patients is previous antibiotic treatment. A relationship between this fact and treatment over the last 12 months has been observed with 3rd-generation cephalosporins, quinolones and imipenem. *P. aeruginosa* is the third most prevalent Gram-negative bacillus (9-13%) but remains far behind *E. coli* Its importance is anecdotal in community infection (3%)[7].

Due to its special pathogenicity and opportunistic yeast condition, the participation and causality of *Candida* spp. in IAI has been widely debated. *Candida* spp. colonises the surgical patient with high frequency (72%) and appears more frequently in IAI cultures of nosocomial origin. The isolation of *Candida* spp. in the peritoneal cavity is observed in 20-30% of secondary peritonitis and its presence could imply a poor prognosis.

The prevalence of invasive fungal infections in patients undergoing gastrointestinal surgery has increased in recent years. There are numerous risk factors associated with *Candida* peritonitis, the main ones being those that promote *Candida* colonisation and impaired host immunity. Among the most relevant factors are the following: the origin of the peritonitis (perforation of upper gastrointestinal tract), the type of peritonitis (tertiary peritonitis in patients with multiple reinterventions), severe acute pancreatitis, high degree of severity (APACHE> 25 points, septic shock), prolonged paralytic ileus, total parenteral nutrition, prolonged antibiotic treatment, prolonged stay in intensive care unit, presence of catheters and/or drainage systems, and administration of gastric therapy (proton pump inhibitors, anti-H2)[8].

EARLINESS, DURATION AND ANTIBIOTIC TREATMENT

Antibiotic treatment is more effective when started early, as well as when it is adapted to the sensitivity of the IAI pathogens. Cohort studies in patients with severe sepsis have shown that for every hour that the initiation of appropriate antibiotic treatment is delayed, mortality increases by 7.6%[9].

The choice of an effective empiric treatment for IAI remains a challenge. Ineffective empiric therapy is associated with higher rates of therapeutic failure, surgical wound infections, surgical reintervention, and higher mortality rates. The choice of antibiotic requires consideration of the source of the infection, safety or toxicity of the antibiotic, interaction with other drugs, administration guidelines, as well as the microbiological variability and patterns of intrinsic resistance of each hospital or critical care unit. Due the polymicrobial nature of secondary peritonitis, empiric treatment inevitably requires combined treatment to achieve the necessary coverage of both habitual pathogens and unexpected pathogens.

The duration of antibiotic treatment in peritonitis has been extensively debated, without a consensus having been reached. There is evidence that, in the patient with an appropriate immune response and after adequate focus control, the residual inoculum may respond to a shorter antibiotic treatment. Recent studies have demonstrated the usefulness of biological markers in evaluating the response to antibiotic treatment. In a recent multicentre study involving 121 patients using procalcitonin (PCT) as a guide to terminating antibiotic treatment, it was demonstrated that antibiotic treatment can safely be withdrawn on day 5, even in severe patients, provided that the focus is controlled, showing a 50% reduction in the duration of antibiotic treatment[10].

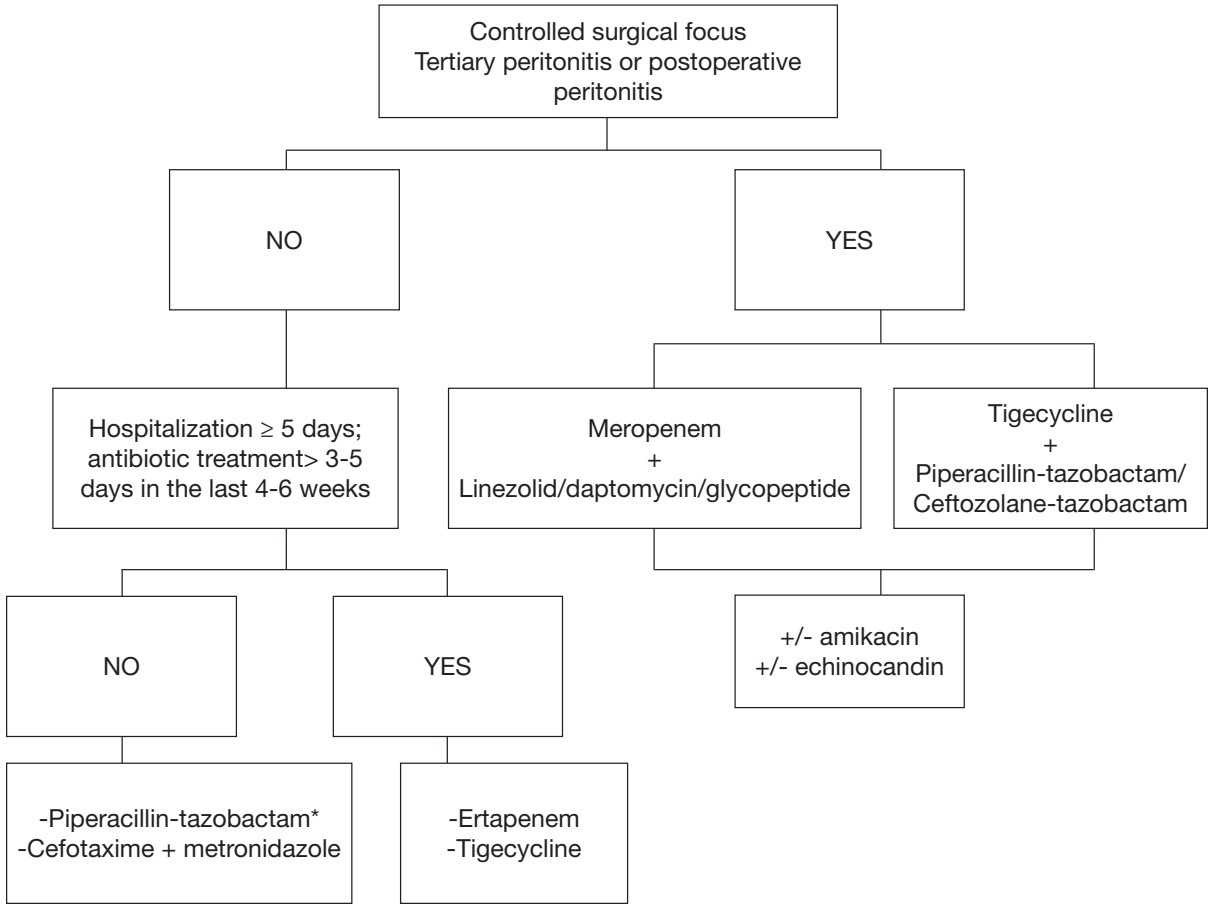

Figure 1 | **Secundary peritonitis. Empirical treatment**

Regarding empirical treatment (figure 1), we must bear in mind that any proposed antibiotic treatment regimen should cover anaerobic microorganisms. A standard treatment regimen is the combination of beta-lactams with beta-lactamase inhibitors, as is the case with piperacillin/tazobactam, which shows activity against *P. aeruginosa*. However, ESBL-producing strains show rates of resistance to piperacillin/tazobactam (according to EUCAST cut-off points) of 27.4% for *E. coli* , of 38.1% for *K. pneumoniae*[11] and 8% for *P. aeruginosa*[12]. New combinations of beta-lactams/ beta-lactamase inhibitors, such as ceftozolane/tazobactam[13] or ceftazidime /avibactam[14] have been developed. Currently available data on the efficacy of these new antibiotics in the treatment of IAI (both administered with metronidazole) are relatively limited, although they show promising data in the treatment of secondary peritonitis (where *P. aeruginosa* may be involved), as part of combined guidelines that include an antimicrobial with activity against anaerobes and against enterococci and/or methicillin-resistant *Staphylococcus aureus* (MRSA) when necessary.

Carbapenems have been recommended as the antibiotics of choice in the empiric treatment of infections caused by multi-drug resistant pathogens, being the first choice when an infection is suspected to be produced by ESBL-producing Enterobacteriaceae or AmpC hyperproducers. However, the excessive use of carbapenems has led to the appearance of carbapenemase-producing *Enterobacteriaceae* (EPC), leaving tigecycline (with activity against multi-drug resistant bacteria) and colistin as therapeutic options. Tigecycline (in high doses) has been included in combined antibiotic regimens for the treatment of secondary peritonitis in critically ill patients, with favourable clinical outcomes[15]. Combined antibiotic treatment guidelines that include tigecycline are an alternative to carbapenems, not only because of their activity but also to avoid the spread of carbapenemases that may compromise the future activity of carbapenems.

Empiric treatment against MRSA is recommended in hospitalised patients or those in long-term healthcare facilities colonised by MRSA, or those at risk of infection due to prior

antibiotic exposure. MRSA is also frequently isolated in difficult-to-treat infections with poor outcome and should be covered in patients with tertiary peritonitis[16]. Vancomycin shows activity against enterococci and MRSA, but it is necessary to consider the tolerance of these microorganisms against the antibiotic, mainly *E. faecium*. These facts compromise the effectiveness of vancomycin, making necessary the use of other antibiotics with activity against Gram-positives such as daptomycin or linezolid and that are recommended in the different clinical guidelines.

Mortality rates for *Candida* peritonitis are very high. The control of the infectious focus, together with the establishment of an early and appropriate antifungal treatment are determinant factors in this. There is sufficient evidence in the literature to support the use of empiric antifungal therapy in patients with secondary peritonitis of nosocomial origin and tertiary peritonitis, since the prognosis of these patients worsens with the isolation of *Candida* in peritoneal fluid[17].

The antifungal treatment of choice in critically ill patients with *Candida* peritonitis should be established by the administration of an echinocandin in the following cases: presence of haemodynamic instability, previous treatment with azoles, existence of fluconazole-resistant *Candida* isolate (peritoneal fluid) or need of renal replacement therapy. Echinocandins should be de-escalated to azoles in those patients in whom antifungal treatment was initiated early, azoles-susceptible strains were isolated and have clinically improved after surgery[17].

CONCLUSIONS

The choice of an appropriate empiric therapy for IAI is vital. It requires knowledge of the intrinsic microbiological variability of each hospital or critical care unit, as well as the source of infection, safety or toxicity of the antibiotic, interaction with other drugs, the dosage guidelines and the presence of risk factors. The use of any antimicrobial carries with it the potential development of tolerance or resistance from the first moment that it is used. Antibiotic resistance in Gram-negative bacteria is increasing exponentially worldwide. There are few clinical trials available that provide us with information on decision making. While we wait for new antibiotic combinations to become available in our centres, optimisation of antibiotic treatment as well as a rational use of it is required.

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Urinary tract infections in inpatients: that challenge

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ABSTRACT

Urinary tract infection (UTI) is one of the major nosocomial infections. In more than 80% of cases it is related to the use of urological devices, especially linked to the misuse of urinary catheters. Empirical treatment should be based on local epidemiology, severity criteria and risk of multiresistant bacteria. This review shows the most important aspects of nosocomial UTI, as well as the recommendations for correct treatment adjustment; both empirical and definitive, that is the great challenge to avoid multiresistance, as well as to avoid unnecessary treatments.

Key words: Urinary Tract Infections, Nosocomial Infections, Antimicrobial Treatment.

Las infecciones del tracto urinario en el paciente ingresado: ese reto

RESUMEN

La infección del tracto urinario (ITU) es una de las principales infecciones nosocomiales. En más del 80% de los casos está relacionada con el empleo de dispositivos urológicos, sobre todo, con el mal uso de las sondas vesicales. El tratamiento empírico debe estar basado en la epidemiología local, criterios de gravedad y riesgo de bacterias multirresistentes. Esta revisión muestra los aspectos más importantes de la ITU nosocomial, así como las recomendaciones para el correcto ajuste del tratamiento; tanto empírico, como dirigido, ese es el gran reto para evitar la multirresistencia, así como evitar los tratamientos innecesarios.

Palabras clave: Infecciones del Tracto Urinario, Infección Nosocomial, Tratamiento Antibiótico.

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IMPORTANCE

Urinary tract infections (UTI) are a well-known cause of nosocomial infection. They are the third most common infection occurring in admitted patients after surgical site and respiratory infections in our country. Urinary catheters (UC) are the most important contributors to nosocomial UTI. According to the *Estudio de la Prevalencia de la Infección Nosocomial en España* (EPINE)[1], 19.0% of inpatients from Spanish hospitals have an indwelling UC. It also shows that 60.2% of nosocomial UTI were associated to UC carriage; and that 7.1% of nosocomial bloodstream infections (BSI) are secondary to nosocomial UTI. As a result, nosocomial UTI not only derives in worse outcomes but also in higher economic costs[2] and antibiotics abuse. Nevertheless, a decrease in the incidence of UTI has occurred during the last years as a result of closed urinary drainage systems.

PATHOGENESIS AND AETIOLOGY

Pathogenesis of UTI is well-known nowadays and two pathways have been described. The first one, the extraluminal pathway, describes a passage of bacteria colonizing the periurethral zone towards the bladder. The intraluminal pathway, on the other side, comprises the introduction of bacteria colonizing the drainage bag or the UC towards the urinary tract. Formation of biofilm facilitates this bacterial progression.

Regarding the aetiology, multiple studies have addressed this issue. Results by Andreu et al[3] show *Escherichia coli* is the most common causal agent of non-complicated cystitis (86%) and up to 90% of non-complicated pyelonephritis. However, complicated UTI have a more varied aetiology. *E. coli* remains the main causal pathogen but other Gram-negative bacilli like *Klebsiella*, *Citrobacter* and *Enterobacter* spp. cause 11%; and *Pseudomonas aeruginosa*, 8%. Gram-positive bacteria also have a role in urinary catheter-associated urinary tract infections (CAUTI) with D-group *Streptococci* causing 19% of them,

and *Staphylococcus aureus*, 4%. Polymicrobial UTI cases represent 30%. Other microorganisms such as yeasts cause 18% of UTI.

Horcajada et al[4] published in 2013 the different aetiology in bacteraemia secondary to UTI in hospitalized patients comparing community, nosocomial and healthcare-associated acquisition, being significant the appearance of *P. aeruginosa* in those of nosocomial origin and extended-spectrum beta-lactamase (ESBL) as well as quinolone-resistant Enterobacteriaceae in those having healthcare-associated acquisition.

DIAGNOSIS

Diagnosis of CAUTI requires the isolation of no more than two species of organisms, at least one of which is a bacterium of $\geq 10^5$ CFU/ml from urine cultures. Present symptoms or signs must include at least one of the following: fever, hypothermia, suprapubic tenderness, or systemic signs without another explanation, like mental status alteration or systemic response inflammatory syndrome. Neither dysuria nor altered urinary frequency nor urinary urgency are valid for this diagnosis. Patients must have had an indwelling UC for more than 2 days on the date of event or a UC that was removed the day before the date of event to be considered as catheter-associated[5].

Asymptomatic bacteriuria, on the other hand, is the growth of more than 10^5 CFU/ml of one usual urinary tract pathogen without any symptoms.

Urine sediments have a high negative predictive value when there is absence of pyuria. Blood cultures are positive only in 30-40% of pyelonephritis. New tools are emerging such as polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) or an old tool such as performing a direct antibiogram from the urine. They can also be useful when a multidrug resistant (MDR) microorganism is suspected to establish an optimal empirical treatment. For UTI complications, imaging like computed tomography and echography have been proven as useful.

PREVENTION

Numerous guidelines to prevent CAUTI have been published in the two last decades. Most of them highlight the importance of educational measures for all healthcare professionals[6]. Hand hygiene is the most important one. Once a patient is found to be either colonized or infected, contact precautions are needed, as well as performing a good environmental cleaning to avoid the MDR transmission.

Limiting unnecessary catheter insertion and reducing catheterization duration are relevant prevention strategies[7]. In a prospective study that described 202 hospitalized patients with urinary catheter, the initial indication was judged to be inappropriate in 21%, and continued catheterization was judged to be inappropriate for almost one-half of catheter-days[8]. Surveillance of an indwelling UC is important too. Saint et al[9] reported a nation-wide study where 56% of hospitals did not have a system for monitoring which patients had urinary catheters placed, and 74% did not monitor duration of catheterization. Furthermore, a French prospective intervention study, showed a reduction in the frequency of CAUTI from 10.6 to 1.1 episodes per 100 patients, when nurses and physicians were reminded daily to remove unnecessary urinary catheters four days after insertion[10]. It also decreased the incidence of CAUTI from 12.3 to 1.8 per 1000 catheter-days. Lately, alternative prevention strategies to consider after catheter insertion like antimicrobial-coated catheters, catheter irrigation with antimicrobials, antimicrobials in the drainage bag or prophylaxis with cranberry products have been proposed. However, data are insufficient to make a recommendation about whether to use them.

TREATMENT

First, asymptomatic bacteriuria should be treated only in certain cases[11] such as pregnant women, before transurethral resection of the prostate or any traumatic genitourinary procedures associated with mucosal bleeding, immunosuppressed patients, or after the first year of renal transplantation. We should consider treating non-pregnant women if there is asymptomatic bacteriuria in the first 48 hours after UC sample. In other cases, antibiotics only eliminate bacteriuria transitorily and their administration neither decreases the frequency of symptomatic infection nor prevents further episodes of asymptomatic bacteriuria. This may also select MDR microorganism.

For symptomatic bacteriuria, before initiation of antibiotics and take of a new urine sample, we must withdraw or replace the UC[12]. To choose an adequate empirical treatment, we should consider the underlying conditions and the local epidemiology (risk of MDR). Carbapenems should be used in patients with high risk of MDR microorganisms as empirical treatment. Quinolones have a resistance of up to 20% in our country. This is important to highlight as it is not recommended to administer empirical antimicrobial treatment with antibiotics having more than 20% of resistant strains for non-complicated UTI or 10% for complicated ones. Treatment must be adjusted once an antimicrobial susceptibility is ready. Other antimicrobial agents are used depending on the aetiology (yeasts or other bacterial species). If a yeast is suspected, fluconazole is the first line antifungal. Amphotericin B is recommended only when fluconazole resistance is suspected. Overall, optimal treatment duration has been classically 14 days, but this can be shortened up to 5 days if there is an adequate clinical response. Follow-up urine cultures are not needed except if there is no clinical improvement 72 hours after treatment start.

MDR microorganisms have emerged during the last years as potential threats to infection control and their treatment can become challenging. Piperacillin/tazobactam is not recommended in monotherapy as empirical treatment of CAUTI if a MDR microorganism is suspected. Carbapenems can be used in monotherapy instead, although higher dose regimens have been suggested. Other options include colistin and disodic

fosfomycin. Rodriguez-Baño et al[13] comparing carbapenems with β-lactams/β-lactamase inhibitor combinations (BLBIC) for treatment of bacteraemia due to ESBL *E. coli*; did not find any significant differences in urinary bacteraemia mortality between carbapenems and BLBIC administered as definitive or empirical treatment. For the treatment of carbapenemases (CBP) Enterobacteriaceae; Tumbarello et al[14] presented a multicentre cohort including 661 adults with bloodstream or non-bacteraemic infections like UTI caused by a CBP *Klebsiella pneumoniae*. They found combination therapy with at least two drugs displaying *in vitro* activity against the isolate was associated with lower mortality. Moreover, combinations that included meropenem were associated with significantly higher survival rates when the meropenem MIC was ≤8 mg/L.

Thus, for the treatment of UTI caused by MDR microorganisms, we suggest either monotherapy or bitherapy should be decided considering severity of underlying conditions, severity of infection, MIC values and clinical response. Monotherapy can be safely used when no severity signs are present. Quinolones and cotrimoxazole can be used safely in definitive treatment only if MIC is optimal given the high frequency of resistance. New drugs like ceftazidime/avibactam and ceftolozane/tazobactam have irrupted in the last year, their role in handling UTI caused by MDR bacteria needs further studies.

CONCLUSIONS

CAUTI still represents a challenging entity in the field of nosocomial infection control. Although improvements to prevent its expansion like closed urinary drainage systems have been made, unnecessary insertion or prolonged urinary catheter remain as important problems, healthcare professionals must be aware of. Treatment must be conducted following certain criteria such as risk factors of severity and MDR and local epidemiology. Of capital importance is not use antimicrobial treatment for all asymptomatic bacteriuria and considering adjustment of treatment once an aetiology and antimicrobial susceptibility has been found to avoid unnecessary antimicrobial treatment and prevent the multiresistant microorganisms.

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Non-valvular intravascular device and endovascular graft-related infection

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ABSTRACT

In the last few years there has been an increase of implantable cardiac electronic device and vascular graft related infections. This is due in part to a higher complexity of some of these procedures and an increase in patient's comorbidities. Despite wide diagnosis methods availability, early stage diagnosis usually constitutes a challenge as often patients only denote insidious symptoms. In most confirmed cases, removal of the infected device is required to resolve the infection. This is mostly explainable because of bacterial ability to grow as biofilms on biomaterial surfaces, conferring them antimicrobial resistance. If removal is not possible, chronic suppressive antimicrobial therapy could be an option.

Key words: Prosthesis-related infections. Vascular graft. Bacterial infection.

Infecciones relacionadas con dispositivos intravasculares no valvulares e injertos endovasculares

RESUMEN

En los últimos años se ha producido un aumento de las infecciones relacionadas con los dispositivos electrónicos cardíacos implantables y los injertos vasculares. Esto se debe en parte a la mayor complejidad de algunos de estos procedimientos y al aumento de comorbilidades en los pacientes tratados. A pesar de la amplia variedad de métodos diagnósticos disponibles, la detección de las infecciones asociadas a estos biomateriales constituye un reto. En la mayoría de los casos es preciso retirar los dispositivos para lograr la curación. Esto se debe en gran medida a la capacidad de las bacterias para desarrollar biopelículas sobre su superficie, lo cual les confiere una enorme resistencia a los antibióticos. Si la retirada no es posible, el tratamiento antibiótico supresor crónico podría ser una opción.

Palabras clave: Infecciones protésicas. Injerto vascular. Infección bacteriana.

INTRODUCTION

In the recent years an increasing number of medical devices have being placed in our hospitals[1]. Despite surgical advances and improvements in biomaterials and design of implantable cardiac electronic devices and vascular grafts, related infection continues to be a major related complication[2]. Ability of bacteria to form biofilms on the biomaterial surface represents one of the main issues involved in the pathogenesis of these infections. Biofilms confers microorganisms a great resistance to innate host defences and antimicrobial agents, making necessary in most cases to explant the infected device to solve the infection[1].

We will review infections related to implantable cardiac electronic devices (ICEDs) [permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy devices (CRT)] and vascular grafts.

EPIDEMIOLOGY

Implantable cardiac electronic devices (ICEDs). Implantation rates of ICEDs in developed countries are increasing as a consequence of new technological advances and wider patient eligibility criteria[3]. Likewise, an increase in ICED related infections has been reported[4] in relation with a rise in the performance of more complex procedures and in the proportion of patients with severe comorbidities, including organ system

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failure (i.e., renal, respiratory or cardiac) or diabetes[3]. Overall, incidence of related infection is estimated to range between 0.5% and 5.7%, being more frequent among ICD/CRT when compared to PPM, and for revision procedures when compared to primary implantation[2,3]. Implantation of devices in the abdominal wall or by a thoracotomy route represent other factor related to a higher incidence of infection, in comparison with those devices implanted at the pectoral site or transvenously[3]. Several studies have evaluated the potential risk factors for ICEDs related infection. Among the most consistently identified risk factors are the number of prior procedures, their complexity and the lack of antimicrobial prophylaxis[3]. Microbial epidemiology of ICED infections is characterized by a predominance of gram-positive bacteria (67.5-92.5%), with coagulase-negative staphylococci (CoNS) representing the most common isolated bacteria followed by *Staphylococcus aureus*. Gram-negative bacilli are isolated in 1% – 17% of patients, with fungal infections representing less than 2% of patients. Polymicrobial infections range from 2% to 24.5%. Culture negative infections range from 12-49%[3].

Vascular graft infections (VGIs). Advances in surgical techniques and graft design (e.g., use of native venous or arterial tissues) have leaded to a reduction in frequency and severity of VGI. However the number of vascular grafts procedures has risen, especially among patients with multiple comorbidities, increasing the risk of related infections and complications. Major complications of VGI are sepsis developement, disruption of infected anastomotic suture with rupture or pseudoaneurysm formation, vascular-enteric fistulae, embolization of infected thrombi, bacteraemic spread of infection, amputation and death[5].

VGIs can be categorized in two groups based on their location: extracavitary (primarily in the groin or lower extremities) and intracavitary (primarily within the abdomen or thorax). Despite this initial classification, frequency of VGI for each group changes in relation with graft anatomic location. For most extracavitary grafts the infection rate is 1.5% to 2%, however it rises to 6% for groin grafts. For intracavitary grafts, infection rate ranges from 1% to 5%, with 1% to 2% of aortic graft erosion or fistulisation to the bowel[5].

Evidence about risk factors associated with VGIs is scarce. *S. aureus* nasal colonization, end-stage renal disease, groin incision, lower limb arterial bypass grafting, postoperative bacteraemia and wound infection have been identified in some studies[6].

Distribution of microorganism responsible for VGIs is as follow: Gram-positive cocci 75%, Gram-negative 9%, polymicrobial infection 7% and culture negative infections 7%. Among Gram-positive cocci infections, CNS are the most common isolation, followed by *S. aureus*. The most common cause of Gram negative-infection is *Pseudomonas aeruginosa*[5].

DIAGNOSIS

Implantable cardiac electronic devices (ICEDs). Diagnosis of ICED infections constitutes a challenge as patients often show insidious symptoms that are usually disregarded. Any combination of the generator pocket, device leads and endocardial structures can be a clinical presentation, being those affecting endocardial structures those associated with a higher mortality[4].

a) Clinical diagnosis. Current guidelines categorized ICEDs infections as early post-implantation inflammation, uncomplicated and complicated generator pocket infections, ICED-infective endocarditis (ICED-IE) and ICED-lead infections (ICED-LIs)[3,4] (table 1).

b) Imaging diagnosis.

Chest radiography/CT scanning. Both tests could contribute to diagnosis providing additional information as the presence of embolic foci of infection or generator migration[3].

Echocardiography. It should be carried out as soon as possible if endocarditis o lead involvement is suspected. This technique is able to establish the presence of endocardial or lead involvement and consequent complications (e.g., new valve regurgitation, abscess formation, etc.). Despite transeoesophageal echocardiography (TEE) has a higher sensibility to diagnose ICED-LI or ICED-EI than transthoracic echocardiography (TTE), both techniques are complementary. Information provided by echocardiography should be interpreted in conjunction with clinical data because masses can be present in non-infected leads and infection could be present in the absence of vegetations[3].

FDG positron emission tomography/computed tomography (PET/CT). Current guidelines discourage routinely use of FDG PET/CT in clinical practice[3] until strong evidences are obtained. Hybrid PET/CT imaging allows a correct fusion of both sets of metabolic and anatomical data, contributing to an easier interpretation[7]. Several studies have evaluated accuracy of FDG PET/CT to diagnose ICED related infections suggesting a substantial improvement in sensibility and specificity. Scarce utility has been suggested for this technique if associated native valve infection is suspected because of the high false negative results in some series[8].

c) Microbiological diagnosis. Blood cultures are the main microbiologic tool for diagnosis of ICED infections during the initial evaluation. Blood cultures are positive in 15-30% of generator pocket and device leads related infections. However, when endocardial structures are involved, this percentage increases[2]. Cultures obtained from pus or tissues from a generator pocket wound are recommended in generator and leads device infection. At the time of device removal, lead fragments (ideally distal and proximal), lead vegetation, generator pocket tissue and the explanted device should be cultured after sonication in order to retrieve biofilm bacteria. If the results are negative, specimens should be submitted for fungal and mycobacterial cultures or amplification and sequencing of bacterial 16S ribosomal RNA genes in order to detect atypical causes not detected by routine cultures[2-4,9].

Vascular graft infections (VGIs).

a) Clinical diagnosis. Clinical presentation of VGIs de-

Table 1 **Definitions of ICEDs infections.**

Early postimplantation inflammation	Erythema affecting the box implantation incision site, without purulent exudate, dehiscence, fluctuance or systemic signs of infection within 30 days of implantation. Includes a small, localised area (<1 cm) of erythema and/or purulence associated with a suture ('stitch abscess').
Uncomplicated generator pocket infection	Any one of: Spreading cellulitis affecting the generator site. Incision site purulent exudate (excluding simple stitch abscess). Wound dehiscence. Erosion through skin with exposure of the generator or leads. Fluctuance (abscess) or fistula formation. AND no systemic symptoms or signs of infection AND negative blood cultures.
Complicated generator pocket infection	As for uncomplicated generator pocket infection but with any one of: Evidence of lead or endocardial involvement. Systemic signs or symptoms of infection. Positive blood cultures.
ICED-lead infection (ICED-LI)	Symptoms and signs of systemic infection without signs of generator pocket infection but with: Definite ICED-LI—either: Echocardiography consistent with vegetation(s) attached to lead(s) and major modified Duke microbiological criteria or Culture, histology or molecular evidence of infection on explanted lead. Possible ICED-LI—either: Echocardiography consistent with vegetation(s) attached to lead(s) but no major modified Duke microbiological criteria or Major modified Duke microbiological criteria but no echocardiographic evidence of lead vegetation(s).
ICED-associated infective endocarditis (ICED-IE)	All of: ICED in situ. Modified Duke criteria for definite infective endocarditis. Echocardiographic evidence of valve involvement.

Adapted from Harrison et al[4].
ICED: Implantable cardiac electronic devices; ICED-LI: ICED-lead infection; ICED-IE: ICED-associated infective endocarditis.

pends on location of graft infection, time since surgery and microorganism responsible for the infection[5]. Several classifications of VGIs have been proposed. One of the most used was proposed by Samson et al[10] (table 2).

Extracavitary

· *Early onset VGIs (<2 months post-surgery)*

It is characterized by an acute presentation with fever, chills and other signs of systemic sepsis, wound erythema, erosion of the graft through the wound, abscess, sinus tract drainage, graft occlusion, peripheral septic emboli, pseudoaneurysm formation, anastomotic rupture with haemorrhage and poor tissue incorporation of the graft[5].

· *Late onset VGIs (>2 months postoperation)*

The clinical course use to be indolent associating local groin erythema, pain, swelling, sinus tract drainage, pseudoaneurysm at the anastomosis or skin erosion[5].

Intracavitary

· *Intraabdominal VGIs*

The clinical presentation includes fever, abdominal pain, failure to thrive, erosion with fistulous enteric communication and sepsis. No obvious physical findings could be identified[5].

· *Intrathoracic VGIs*

In cases of infection affecting aortic roof, symptoms could mimic an infectious endocarditis with fever, chills and heart failure. Other clinical presentations may include septic emboli or sudden massive haemorrhage secondary to anastomotic rupture, oesophageal or bronchial fistula[5].

b) Radiologic diagnosis

Ultrasound. It constitutes a cheap and innocuous imaging procedure of interest especially in patients with suspected extracavitary VGIs. Ultrasound can be performed at patient´s bedside allowing puncture of potentially cultivable collections and identification of pseudoaneurysms. A low utility for intracavitary VGIs has been reported. Echocardiography should be indicated for patients with suspected intrathoracic VGIs[5].

CT/CT angiography (CTA). It is useful in cases of extravascular VGIs suspicious, representing the elective procedure in

Table 2 Samson classification for extracavitary VGIs

Grade	Definition
Samson I	Infection (purulence and bacteria) extended no deeper than the dermis of the wound containing the arterial prosthesis.
Samson II	Infection (abscess, fluid collection) involved subcutaneous tissue but did not come in grossly observable direct contact with the graft.
Samson III	Infections involved the body of the graft but not an anastomosis.
Samson IV	Infections surrounded an exposed anastomosis but bacteraemia or anastomotic bleeding had not occurred.
Samson V	Infections involved a graft-to-artery anastomosis and were associated with septicemia with positive blood cultures and/or anastomotic bleeding at the time of presentation or, at the time of wound excision, by evidence of arterial wall softening such as loose sutures or discoloration of the artery at the anastomosis.

Adapted from Samson et al[10].

cases of intracavitary VGIs. CTA is useful to define extend of infection, to evaluate vascular anatomy (providing valuable information for surgical planning) and to identify fluid collection eligible to be puncture for culture[5]. Suggestive signs of VGIs include ectopic gas present beyond 4-7 weeks and perigraft fluid with fat stranding beyond 3 months after implantation[6].

CT/CTA require iodinated contrast iv administration with a potential kidney toxicity, so it should be avoided in patients with renal failure despite loose of diagnostic capacity. Otherwise implantable medical devices induce image degradation, making harder to evaluate the image. In case of suspicion of gastrointestinal bleeding related to intra-abdominal VGI performance of CTA in combination with esophagogastroduodenoscopy are recommended[5].

Magnetic resonance image (MRI). It is indicated if CTA result inconclusive. It is more expensive and requires more time to be done but offers higher soft tissue resolution. MRI may differentiate between hematoma, inflammation and infection, identifying potential mycotic aneurisms, bleeding or aortic fistulas. MRI requires infusion of gadolinium iv contrast that may cause a fibrosing dermopathy in patients with pre-existing renal failure. As disadvantages, guide punctures collections could not be done and its use is limited in patients with intracardiac electronic devices[5].

Nuclear medicine studies. Characterized by high cost and scarce availability.

· *Indium labelled white blood cell scan (In-scan)*

It is recommended in combination with other imagine techniques (e.g., MRI) when previous radiologic test result indeterminate. There is no risk of renal impairment after contrast administration. It requires more than 24 hours to obtain results. It is less sensitivity if patient is under or recently received antibiotic treatment, with high risk of false positive results in early postoperatory patients[5].

· *FDG PET/CT*

It may be indicated if previous radiologic exams are indeterminate. Scarce evidences are available about its role for VGIs diagnosis but it seems to be useful. Among proposed predictors of VGIs, focal FDG uptake on the PET component and irregular graft boundary on CT has been related to a positive predictive value of 97%. False positive results have to be considered, especially if no other clinical or laboratory evidence of infection is present (i.e., aseptic inflammatory reaction to synthetic grafts)[5,7].

c) Microbiological diagnosis

Efforts to obtain a representative culture should be done in these cases. Perigraft fluid collection obtained through ultrasound or computed tomography-guided aspiration are usually diagnostic. Cultures from wounds or sinuses must be avoided because isolates may just represent skin-colonizing microbiota and might not accurately reflect the causative microorganism. Blood cultures are often negative in these cases. Intraoperative specimens and complete or partial device are recommended to be cultured after a sonication procedure or analysed with molecular techniques[2,5,6].

TREATMENT

Implantable cardiac electronic devices (ICEDs)

a) Early post-implantation inflammation. This entity does not constitute a confirmed infection. Device removal is not required, but a close follow up should be done. Empirical antimicrobial therapy may be started for 7-10 days based on clinical decision, although the role of antibiotics is unclear[3].

b) Uncomplicated and complicated generator pocket infection. Preferred treatment option includes removal of the whole system as soon as possible (i.e., <2 weeks from diagnosis) followed by a 10-14 days of antimicrobial treatment. In those patients with absolute ICED requirement, a temporary pacing should be used until reimplantation (i.e., once symptoms and sings of systemic and local infection are resolved). If lead removal is not an option because risk are considered too high or because patient declines, then, generator should be removed leaving leads in *situ* and followed by a 6 week iv

antibiotic course treatment. As it was previously mentioned, the role of persisting biofilms in the remaining biomaterial increases the risk of relapse. Patients with absolute requirement for ICED requiring a newly implanted system, are at high risk of re-infection. In case of terminally ill or exceedingly frail patients chronic suppressive antimicrobial therapy might be the best option[3].

c) ICED-lead infection (ICED-LI). Complete device removal followed by antibiotic treatment is the preferred option. Percutaneous procedures are preferred over open surgery for ICED removal. Duration of antimicrobials should be established based on clinical response. Short course of antibiotic therapy (2 weeks) should be considered, reevaluating therapy 1 week after device removal. In case of tricuspid valve lesions, ghost lesions after system removal, or an inappropriate clinical response, patient should be treated as having ICED-IE[3,4].

d) ICED-associated infective endocarditis (ICED-IE). As for previous ICEDs infections, prompt and complete device removal followed by iv antibiotic treatment constitutes the headstone of treatment. Duration of treatment vary according to the characteristics of the affected valve, ranging from 4 weeks for native valves to 6 weeks for prosthetic valves or extra-cardiac foci of infection (i.e., secondary brain abscess or spinal infection)[3].

For ICED-LI or ICED-IE in which device removal is considered too risky or refused by patient, salvage therapy with a prolonged course of iv antibiotic therapy could be attempted. Antibiotics should be discontinued after 6 weeks. Close follow up should be continued because the high risk of relapse of this treatment option. In case of relapse, long-term oral suppressive therapy should be started[3].

Vascular graft infections (VGIs)

a) Extracavitary VGIs. The absence of specific guidelines makes difficult a standardization of surgical therapy for extracavitary VGIs. Some authors propose the use of the Samson classification to define the extent of VGI, establishing specific medical and surgical recommendation for each group[5].

- Samson I

It should be treated as a soft tissue infection without involvement of graft tissue. Initial empiric antibiotic treatment should be initiated until specific microorganisms are identified with a 2-4 weeks antimicrobial course. Excision, drainage or debridement is not generally required[5].

- Samson II

Antibiotics should be used as for Samson I, but patients usually require surgical debridement including muscle flap or use of vacuum-assisted closure (VAC) device to promote wound coverage[5].

- Samson III

Better outcomes have been reported with graft preservation for patients with Samson III early onset VGIs, with graft resection and in situ reconstruction being recommended for Samson III late onset VGIs. Among in *situ* reconstruction techniques are rifampin-bonded or silver-coated synthetic vascular grafts, cryopreserved or fresh arterial allografts, and autogenous venous grafts. Antibiotic treatment should be accomplished for 4-6 weeks (oral or IV), considering a 6 weeks to 6 months period of additional oral therapy based on individual patient risk[5].

- Samson IV

Management of Samson IV VGIs depends on several factors including the involved microorganism and the status of the anastomotic suture. In patients with a failure attempt of graft preservation or in situ reconstruction, or when *P. aeruginosa* or a multidrug-resistant microorganism is involved, it is preferable to perform an extra-anatomic revascularization followed by graft excision. A muscle flap is recommended for wound coverage with or without use of VAC device for intermediate steps. The antibiotic regimen might be as for Samson III[5].

- Samson V

Extra-anatomic revascularization followed by graft excision is the preferred option for this group of patients, with the exception of those with a solid contraindication for the surgical procedure (i.e., high operative risk, no viable revascularization options, short life expectancy). A 4-6 weeks course of iv antimicrobials is recommended followed by at least 6 months of oral therapy[5].

Long-term suppressive antimicrobial therapy should be an option in cases of infection with difficult to eradicate microorganisms, emergency or multiple surgeries, graft preservation or in situ reconstruction with extensive perigraft infection or patients not eligible for reoperation[5].

b) Intracavitary VGIs

- *Intraabdominal*

Graft excision and in situ reconstruction with cryopreserved arterial allograft, venous autograft or rifampin-bonded synthetic graft constitute the preferred surgical option in patients with or without aortoenteric fistula. Recommended duration of parenteral antibiotic regimen after surgery is 6 weeks. Based on individual risk factors of patients, an additional course of oral antibiotic treatment should be considered for 3-6 months[5].

In those patients with extensive intraabdominal abscesses, perigraft purulence or VGIs caused by MRSA, *Pseudomonas* spp., or multidrug–resistant microorganisms, performance of an extra-anatomic bypass revascularization followed by graft excision represents the elective procedure. After a conventional course of antibiotic, lifelong suppressive antimicrobial therapy may be considered[5].

- *Intrathoracic*

Intrathoracic VGI without an oesophageal or bronchial fistula used to affect patients with a synthetic arterial allograft. In these cases, in *situ* repairment using cryopreserved or fresh arterial allografts is reasonable. To promote healing and

to reduce infection, coverage of the new allograft with a muscle flap or omentum is recommended[5].

Unstable patients with oesophageal or bronchial fistula usually require in *situ* graft replacement. In selected patients ascending aorta–to–upper abdominal aortic bypass could be an option, with removal of the infected graft, debridement of devitalized tissues and closure of the ends of the aorta. Extra-anatomic reconstruction is rarely an option. To cover the new graft or aortic stumps with omentum, muscle flap or other components are important surgical adjuncts[5].

Parenteral antibiotic treatment for 4-6 weeks is recommended. Based on the risk of infection recurrence, a prolonged course of antibiotic treatment (i.e., 3-6 months) or lifelong suppressive antimicrobial treatment should be considered[5].

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New sepsis criteria: do they replace or complement what is known in the approach to the infectious patient?

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ABSTRACT

There have recently been profound changes in both the definitions of sepsis and septic shock and the diagnostic criteria established for daily clinical practice. In addition, a new screening tool known as qSOFA has been introduced to identify patients at risk of a poor short-term outcome. This score has been accompanied by some controversy due to presenting a lower sensitivity than the systemic inflammatory response criteria previously used to identify such patients. In this article, we shall summarise and analyse the most important recently published studies in relation to these new criteria.

Keywords: sepsis criteria, infection, mortality

Nuevos criterios de sepsis: ¿sustituyen o complementan lo conocido en la aproximación al enfermo infeccioso?

RESUMEN

Recientemente se han producido cambios profundos tanto en las definiciones de sepsis y shock séptico como en los criterios diagnósticos establecidos para la práctica clínica diaria. Además, se ha introducido una nueva herramienta de cribado para la identificación de pacientes con riesgo de malos resultados a corto plazo, el qSOFA. Esta escala se ha acompañado de cierta controversia al presentar una menor sensibilidad que los criterios de respuesta inflamatoria sistémica utilizados previamente para la identificación de estos pacientes. En el presente trabajo resumimos y analizamos los estudios más importantes recientemente publicados en relación con estos nuevos criterios.

Palabras claves: criterios de sepsis, infección, mortalidad

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INTRODUCTION

New criteria have recently been adopted to define sepsis. In this article, we shall review the causes that triggered the need to redefine this syndrome, the reason for the established definitions, and the problems and criticisms which have arisen as a result.

THE PROBLEM OF PREVIOUS DEFINITIONS

From the pathophysiological point of view, sepsis determines alterations in the metabolic pathways and cellular and circulatory alterations, which cause an increase in the mortality of the infected patient[1]. Previous definitions of sepsis were based on and reflected systemic manifestations of infection, which conceptually does not have to imply such pathophysiological alterations or necessarily indicate an abnormal host response to infection. Systemic inflammatory response syndrome (SIRS), used for the diagnosis of sepsis up to now, may simply reflect an adaptive and transient response. In other words, it reflects the host's inflammatory response to infection, but does not necessarily indicate an abnormal response with risk of death[2,3].

Meanwhile, SIRS criteria are present in many hospitalised patients who do not present with infection or poor clinical evolution[4,5]. In short, the problem was that the previous definition of sepsis did not always reflect a risk situation in an infected patient.

THE PROPOSED SOLUTION TO THE PROBLEM

The new definitions state that sepsis is a potentially life-threatening organic dysfunction, caused by an abnormal host response to infection[6]. In this sense, focus is given to the importance of the non-homeopathic host response to infection, the potential lethality, which greatly exceeds that of an

Table 1 **Studies that evaluate the prognosis scores in infected patients.**

Author	Design	Population	Mortality	False Negat. [n(%)]	SIRS	qSOFA	SOFA	Reference
Seymour CW	R	ED	Hosp.	SIRS: 679 (1.6) qSOFA: 849 (1.5) SOFA: 604 (1.4)	SE: 64 SP: 65 PPV: 5 NPV: 98	SE: 55 SP: 84 PPV: 9 NPV: 98	SE: 68 SP: 67 PPV: 6 NPV: 99	JAMA 2016[8]
Williams JM	P	ED	30-day	SIRS: 74 (1.6) qSOFA: 163 (2.0) SOFA: 80 (1.2)	SE: 77 SP: 54 PPV: 6 NPV: 98	SE: 50 SP: 91 PPV: 18 NPV: 98	SE: 76 SP: 78 PPV: 11 NPV: 99	CHEST 2016[11]
Freund Y	P	ED	Hosp.	SIRS: 5 (2.2) qSOFA: 22 (3.3) SOFA: -	SE: 93 SP: 27 PPV: 11 NPV: 98	SE: 70 SP: 79 PPV: 24 NPV: 97	-	JAMA 2017[10]
Seymour CW	R	ICU	Hosp.	SIRS: 117 (9.3) qSOFA: 103 (4.3) SOFA: 26 (3.7)	SE: 91 SP: 17 PPV: 18 NPV: 91	SE: 92 SP: 34 PPV: 21 NPV: 96	SE: 98 SP: 10 PPV: 17 NPV: 96	JAMA 2016[8]
Raith EP	R	ICU	Hosp.	SIRS: 2.387 (9.8) qSOFA: 11.332 (13.6) SOFA: 793 (4.3)	SE: 93 SP: 15 PPV: 20 NPV: 90	SE: 67 SP: 48 PPV: 23 NPV: 86	SE: 98 SP: 12 PPV: 20 NPV: 96	JAMA 2017[9]

False Negat.: false negatives; SIRS: Systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment; R: retrospective; P: prospective; ED: emergency department; ICU: intensive care unit; Hosp: in hospital; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value

infection, and the need for urgent identification. The importance of including "life-threatening organic dysfunction" in the definition is consistent with the pathophysiology underlying the syndrome: cell defects, and physiological and biochemical abnormalities within specific organ systems. Septic shock is defined as a subset of patients with sepsis where the underlying abnormalities of cellular and circulatory metabolism are deep enough to substantially increase mortality[6].

In order to establish the diagnostic method which reflects these definitions, extensive databases were retrospectively analysed. Patients were categorised according to different known prognostic scores (SIRS, LODS, SOFA) and the main outcome variable was in-hospital mortality[7]. Thus, it was concluded that SOFA was the most parsimonious score to diagnose sepsis, and that the cut-off point of 2 or more was the one that showed the greatest difference of mortality between the groups once the patients were categorised.

The diagnosis of septic shock was defined as the presence of maintained hypotension despite fluid therapy with the requirement of vasopressors and a lactate > 2 mmol/l. These criteria identify a subgroup of patients with sepsis who in the database analysis presented with a significantly higher mortality than the other patients[8].

Although from the conceptual point of view these new definitions have not been criticised, the problem of the methodology used to establish the diagnostic criteria is that it was carried out by means of retrospective analysis of databases where there is an important loss of data in several variables, which could affect the outcomes obtained.

THE PROBLEM OF THE PROPOSED SOLUTION

The problem of diagnosing sepsis based on the SOFA score is that this scale contains analytical variables, which could determine a delay in diagnosis and in the start of treatment, and also restricts the care level where it can be performed. For this reason, the new definitions are accompanied by a new methodology which is useful for the screening of patients at risk of suffering sepsis, namely qSOFA, and in which specific treatment should be initiated pending the analytical results that enable SOFA to be conducted.

The adoption of variables included in qSOFA (respiratory rate ≥22 rpm, altered level of consciousness and systolic blood pressure ≤100 mmHg) as a screening tool is also a consequence of the retrospective analysis of the same databases[7]. In this way, it was observed that, in terms of in-hospital mortality, the combination of these variables presented the best area under the curve (AUC) as opposed to the other scores evaluated in patients not admitted to critical care units.

Several studies have subsequently evaluated the usefulness of qSOFA to identify patients at risk of in-hospital mortality or at 30 days[9-11]. These studies have confirmed that qSOFA is the

best AUC prognostic score to identify the infected patient at risk of mortality. However, when assessing the sensitivity and specificity of the different scales for established cut-off points (≥2 points), we can see the lower sensitivity and greater specificity of qSOFA versus SIRS for the risk stratification of these patients[9-11]. The problem of SIRS has been its use as a diagnostic tool for sepsis, but we should question whether it could be useful as a screening tool[12,13].

At this point, it is worth asking what the purpose of a screening test should be. When the price of omitting the diagnosis is very high, as occurs in serious but treatable diseases, a sensitive test is particularly useful, since it allows the doctor to exclude the possible disease when its outcome is negative[14]. A screening test has no diagnostic purpose. People with positive or suspected findings can be evaluated with a more specific diagnostic test to define or reject the final diagnosis. High specificity is useful for confirming a diagnosis which has been suggested by other data, providing few false-positive outcomes[15].

However, sensitivity and specificity do not answer these two questions: if the test is positive, what is the probability of the individual having the disease?; If the test is negative, what is the probability of it not appearing? To answer these two questions, which we actually pose in regular clinical practice, it is necessary to know the positive predictive value (PPV) and the negative predictive value (NPV)[16].

In this way, and in relation to a screening test which can rule out the presence of a seriously infected patient, in regular clinical practice we are interested in having a high negative predictive value that prevents a significant number of false negatives.

In table 1, we can see the different recently published studies[9-11], which evaluate the various prognostic scores. It can be observed how qSOFA detects a population in emergencies with a higher risk of death (specificity and higher PPV) without losing NPV with regard to SIRS. Despite the lower qSOFA sensitivity, false negatives occur in a similar percentage with both scores.

When we evaluated the studies performed in patients admitted to critical care units, we observed that the NPV of SIRS and qSOFA decreased and the false negatives increased. This is because the outcomes of predictive values are influenced by the prevalence of the disease, in this case by the prevalence of mortality. Being critical patients, mortality is higher and, therefore, the NPV declines. For this reason, the best outcomes in this population are obtained with SOFA.

CONCLUSION

The new definitions of sepsis are conceptually more appropriate than previous ones. SOFA as a diagnostic tool is also more useful as it better identifies an infected population at risk of poor outcomes than SIRS.

For the screening of sepsis, qSOFA has shown less sensitivity than SIRS in populations treated outside critical care units, but with a similar NPV. As it is a simpler score, which does not require any analytical variable and can therefore be performed at any level of care, qSOFA should replace SIRS as a tool to be used to identify at-risk patients.

However, there are certain limitations which may compromise our knowledge to date. We should not forget that the studies which led to these new definitions are retrospective; that there is a large loss of data in important variables in these databases, and even in later prospective studies; and that the results have not been evaluated in special populations, such as immunosuppressed patients or the elderly.

CONFLICTS OF INTEREST

None to declare

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Utility of rapid microbiological techniques for the diagnosis of severe infections

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ABSTRACT

Rapid diagnostic microbiological techniques and antimicrobial susceptibility testing are necessary for early and adequate treatment. The utility of old (Gram stain, antigen detection, direct antimicrobial susceptibility testing, chromogenic media) and new techniques (molecular assays, MALDI-TOF) is summarized for the rapid diagnosis of bacteraemia and fungaemia, catheter-related bloodstream infections, pneumonia, meningitis, skin and soft-tissue infections, urinary tract infection, *Clostridium difficile* infection, viral infections, and tuberculosis.

Key words: rapid diagnosis, rapid microbiological techniques, severe infections, intensive care unit.

Utilidad de las técnicas rápidas de Microbiología en el diagnóstico de los grandes síndromes

RESUMEN

Las técnicas microbiológicas de diagnóstico rápido y de sensibilidad a antimicrobianos son necesarias para instaurar un tratamiento precoz y adecuado. Se resume la utilidad de las viejas técnicas (tinción de Gram, detección de antígenos, antibiograma directo en muestras clínicas, medios cromogénicos) y las nuevas (métodos moleculares, MALDI-TOF) para el diagnóstico rápido de la bacteriemia y la fungemia, bacteriemia relacionada con el catéter, neumonía, meningitis, infecciones de piel y tejidos blandos, del tracto urinario, infección por *Clostridium difficile*, infecciones víricas y tuberculosis.

Palabras clave: diagnóstico rápido, técnicas microbiológicas rápidas, infecciones graves, unidad de cuidados intensivos.

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INTRODUCTION

Rapid diagnostic microbiological techniques and antimicrobial susceptibility testing allow early identification of microorganisms and resistance patterns, which are necessary for adequate clinical and therapeutic management of patients. In patients with severe infections, timely antimicrobial therapy is even more critical to outcomes, and in this setting rapid etiologic microbiological diagnosis is mandatory. The most common and severe infections are bacteraemia and fungemia, intravascular catheter-related bloodstream infections, pneumonia, meningitis, acute skin and soft-tissue infections, urinary tract infections, and *Clostridium difficile* infection. In addition, early diagnosis of tuberculosis and viral respiratory infections allows rapid treatments and avoids the use of unnecessary antimicrobials. This manuscript summarizes some of the rapid techniques used for the diagnosis of these infections.

RAPID DIAGNOSIS OF BACTERAEMIA AND FUNGAEMIA

Bloodstream infections remain a major clinical challenge with a high attributable mortality and are associated with elevated costs. Rapid identification of patients with bacteraemia or fungaemia is critical in influencing antimicrobial therapy[1]. Several molecular assays (SeptiFast®, SeptiTest®, Plex-ID®, among others) based on real-time PCR have been developed and commercialized for the detection of bacteria and fungi directly from blood specimens[1]. These assays include the detection of different series of Gram-positive cocci, Gram-negative bacilli, different species of yeasts and filamentous fungus. Some also include the detection of methicillin and vancomycin resistance genes (*mecA, vanA, vanB*). Recently, a new nanodiagnostic approach, the T2 magnetic resonance assay, is being used for the rapid diagnosis of candidemia in whole blood, and represents a new era of molecular diagnostics[2].

Although molecular assays can reduce the time to detection of specific pathogens in blood to 4 h, blood culture techniques and Gram staining, are still necessary. These techniques are simple and available in all Microbiology laboratories, and despite their shortcomings, blood cultures remain the standard laboratory tests for the diagnosis of bacteraemia and fungaemia. At present, molecular assays lack sufficient sensitivity to be used as standalone tests, and no molecular assay can be a substitute for blood cultures, but can be useful as adjunts to blood cultures[1]. In addition, different systems have been developed for the detection of microorganisms directly from blood cultures. Among these, the microarray-based nucleic acid assays (Verigene®, FilmArray ®) for the detection of bacteria and resistance markers have shown high positive-predictive values, ranging from 95% to 100%, and are potential adjuvant tools for improving the microbiological diagnosis of sepsis[1]. Other nucleic acid amplification tests (Gene Xpert®) can be used for the detection of the *mecA* gene in methicillin-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* and for the detection of the *vanA* gene in vancomycin-resistant strains of enterococci. Antigen detection is another alternative than can be used directly from blood cultures. The BinaxNOW® *S. aureus* test is an immunochromatographic assay that detects an *S. aureus*-specific protein, allowing for differentiation between *S. aureus* and other Gram-positive cocci with 97.6% sensitivity and 100% specificity[1]. In recent years, matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF) has been widely used for the rapid microbial identification from blood cultures. The use of MALDI-TOF reduces considerably the time to identification and results are concordant to the genus level for more than 95% of blood cultures in comparison with conventional identification methods[1]. The peptide nucleic acid-fluorescent *in situ* hybridization (PNA-FISH) method (AdvanDx®) has also been shown to reduce the time to identification of microbial pathogens present in blood cultures, however, this method has only been developed for the detection of a limited number of bacterial and yeast species[1]. Finally, the use of chromogenic media for diagnosing (the colours of the colonies help in the identification) are available for detection of many microbial species and for the detection of extended-spectrum-beta-lactamases-mediated resistance and other mechanisms of resistance. These media also allow rapid detection of polymicrobial bacteraemia or fungaemia when used directly from blood cultures and they are cost-effective by reducing both time and reagents used to identify the organisms[1]. Direct antimicrobial susceptibility testing from blood cultures by the disk diffusion or by the gradient diffusion methods also decreases the time needed for susceptibility test results. Although these methods are not standardized, they are commonly used in many laboratories and provide a rapid and useful information to clinicians.

RAPID DIAGNOSIS OF CATHETER-RELATED BLOODSTREAM INFECTIONS (CR-BSI)

Catheter-related infections are among the most important nosocomial infections, causing at least 20% to 40% of all hospital-acquired bacteraemias. In patients with suspected bacteraemia, a substantial number of tip cultures are negative. The diagnosis of CR-BSI can be performed with or without catheter removal. Semiquantitative cultures of superficial structures (catheter hubs and skin around the insertion point of the catheter) are an easy, rapid, safe, and conservative method for ruling out CR-BSI. With a negative predictive value of 96.7%, this method avoids many unnecessary catheter withdrawals[3]. Other conservative procedures that do not require catheter removal include differential paired quantitative blood cultures using lysis-centrifugation tubes: to compare colony counts in peripheral vein blood versus blood drawn from the catheters (a ratio of ≥3/1 cfu/ml, catheter/peripheral, indicates CR-BSI), and the method named differential time to positivity using a continuous-monitoring automated blood culture system: ≥2 h between a catheter blood culture and a peripheral blood culture indicates CR-BSI[4].

RAPID DIAGNOSIS OF PNEUMONIA

Rapid microbiological diagnosis of hospital-acquired pneumonia and especially ventilator-associated pneumonia (VAP) has a high impact in the prognosis of the disease. Expectorated and induced sputa and tracheal aspirates are the most common specimens submitted for diagnosis of lower respiratory tract infections. Microscopic examination and culture of these samples remain the mainstays of the laboratory diagnosis of pneumonia despite controversy concerning their sensitivity and specificity. Microscopy (e.g., Gram stain, acid-fast stains, calcofluor white stain, specific fluorescent antibody tests for *Pneumocystis jirovecii*) can provide a rapid diagnosis if positive of bacterial and fungal infections, but have low sensitivity, and alternative test methods should also be used when negative. Infections with some respiratory pathogens (*Streptococcus pneumoniae, Legionella pneumophila*) can be diagnosed by detecting specific antigens in urine within 10 to 20 minutes. The nucleic acid assays are becoming the diagnostic tests of choice for the rapid diagnosis of some pathogens including *P. jirovecii*, *Mycoplasma pneumoniae*, and respiratory viruses, including influenza and respiratory syncytial virus[5]. In the case of *Mycobacterium tuberculosis* commercialized molecular tests detect the organism and resistance genes in less than 2 hours. For the specific case of VAP, molecular techniques allow a rapid identification of methicillin-resistant or susceptible *S. aureus* (MRSA and MSSA) by directly subjecting clinical samples to PCR (GeneXpert®) in 1 hour[6]. In addition, the performance of direct gradient susceptibility testing (E-test) on lower respiratory tract samples has proven to be a rapid and accurate procedure for antimicrobial susceptibility testing. By using this method, susceptibility results are available in 18 to 24 h with

a correlation of 96.1% with the standard method[7]. Another approach is a modification of the direct E-test technique using a chromogenic agar medium (Mueller-Hinton base) to generate both rapid antimicrobial susceptibility and organism identification results. Full agreement with the standard procedure was observed in 94.9% of cases[8].

RAPID DIAGNOSIS OF MENINGITIS

Acute meningitis is a medical emergency that requires rapid identification of the aetiologic agent. Gram-staining of the cerebrospinal fluid (CSF) is generally positive for patients with bacterial meningitis (with the exception of infection with *Listeria monocytogenes*), and its sensitivity can be improved by concentrating the specimen by centrifugation when it is received in the laboratory. In recent years, the use of direct antigen tests for bacteria in CSF has little value due to the decrease in the incidence of *Haemophilus influenzae* meningitis and the lack of a reliable *Neisseria meningitidis* serotype B antigen test. However, antigent tests for *Cryptococcus neoformans* are rapid (results can be obtained in 15 minutes), sensitive and specific[5]. Cultures for the most common causes of meningitis are generally positive within 1 to 2 days and, as in the case of VAP, it is also useful the performance of direct gradient susceptibility testing on CSF when microorganisms are present in the Gram-stain. In these cases, susceptibility results are available in 18 to 24 h (unpublished data from the author). The use of multitarget PCR tests for the detection of all bacterial pathogens in CSF provide a rapid (less than 3 hours) and specific diagnosis of meningitis, and some of these are currently available commercially (RealCycler® MENELI). At present, the detection of enterovirus and other central nervous system viruses can also be performed in less than 2 hours by the use of different molecular methods and platforms.

RAPID DIAGNOSIS OF SKIN AND SOFT-TISSUE INFECTIONS

In severe skin and soft-tissue infections, a Gram stain must be performed to obtain some preliminary information of the infecting organism(s). Nowadays, the rapid detection of MSSA and MRSA can be performed directly in wound specimens in 1 hour by using a commercialized multiplex PCR assay (GeneXpert®). The agreement between this assay and the standard culture is >95%[9]. Direct antigen detection tests are highly sensitive and specific for the rapid diagnosis of severe infections caused by *Streptococcus pyogenes*[5].

RAPID DIAGNOSIS OF URINARY TRACT INFECTIONS

Rapid screening techniques for urinary tract infection include direct Gram stain and several commercially available products such as dipstick methods and bioluminescence, among others. Gram-staining of fresh uncentrifuged urine is a cheap, rapid and accurate method for the detection of significant bacteriuria. This method has a negative predictive value of >95%, which shortens the time for reporting a negative culture result. When positive, Gram stain guides antimicrobial treatment. The use of MALDI-TOF mass spectrometry performed directly in urine samples after a positive Gram stain for the identification of bacteria anticipates the culture results in 83% of cases and results can be obtained in 1 hour with 4% of major errors[10]. The use of chromogenic media also allows rapid identification of the most frequent microorganisms causing urinary tract infections. In addition, direct antimicrobial susceptibility testing of urine samples, although criticized because the inoculum is not standardized, has shown a good correlation with standard methods providing results in 24 hours[11].

RAPID DIAGNOSIS OF *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

Clostridium difficile is the most common cause of hospital-acquired bacterial gastroenteritis. The appearance of hypervirulent strains, such as ribotype 027, has contributed to the increased incidence and severity of infection. A variety of diagnostic test methods are available for the rapid diagnosis of *C. difficile* disease. At present, multistep algorithms based on the initial results for glutamate dehydrogenase followed by a sensitive toxin test and/ or a nucleic acid amplification test are best options and results can be obtained in less than 2 hours[1].

BIOMARKERS OF ACUTE BACTERIAL INFECTIONS

Porcalcitonin (PCT), the prohormone of calcitonin, is synthesized by a variety of tissues in response to bacterial infection to a greater extent than to viral infections. A cut-off of PCT >1.39 ng/ml is accurate for diagnosing severe sepsis. Levels of serum procalcitonin are also useful to guide antimicrobial therapy in acute respiratory infections and to reduce the antibiotic use[5,12].

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Optimizing antimicrobial prescribing: a practical decalogue

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ABSTRACT

Increasing antibiotic resistance is one of the leading problems in the Public Agenda worldwide. In the last 20 years, the pace of antimicrobial drug development has markedly slowed leading to a dramatic world situation. Infections with antibiotic-resistant microorganisms have been associated with increased length of stay, mortality and costs. Improving antimicrobial prescribing is one of the tools in our hands to optimize the outcomes of patients with moderate to severe infections and control the emerging of resistance. Several clues to improve antimicrobial prescribing are provided as a key-messages decalogue.

Keywords: antibiotic prescribing, antimicrobial stewardship programs, antimicrobial resistance.

Optimización del uso de antibióticos: Decálogo práctico

RESUMEN

El incremento de resistencias antibióticas es uno de los problemas fundamentales al que nos enfrentamos en el manejo de infecciones en la actualidad. En los últimos 20 años, el desarrollo de nuevos fármacos se ha reducido de manera considerable conduciendo a una dramática situación mundial. Las infecciones por microorganismos multirresistentes se han asociado con un aumento de la estancia hospitalaria, de la mortalidad y de los costes. Para intentar cambiar esta situación, una de las estrategias que disponemos es mejorar el uso de antimicrobianos para disminuir la aparición de resistencias. En el texto se articulan en forma de decálogo mensajes claves para la optimización del uso de antibióticos.

Palabras clave: prescripción antibiótica, programas de optimización antimicrobiana, resistencia antimicrobiana.

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INTRODUCTION

We are witnessing a significant increase in antibiotic resistance to which antibiotic overuse and misuse has contributed. It has been consistently observed across several studies over the last decades that antimicrobials are often used inappropriately in up to 50% of prescriptions[1,2].

Antibiotics are unique drugs since its use in a given patient may impact on others (ecological impact) and, thus, prescribers should be aware of their responsibility in their use.

Antibiotic prescribing should be the result of an individualized, rational and methodical process, which must be conducted considering the available clinical, epidemiological, pharmacological and microbiological information and evidence.

Nevertheless, there are several factors that can negatively affect the prescribing process ("interferences"). First, as antibiotic may be prescribed by almost every physician, prescribers frequently lack the needed knowledge expertise in infectious disease and antimicrobial therapy. Other relevant interferences to the prescribing process are diagnostic uncertainty (for example, in respiratory infections it may be difficult to discern whether the etiological agent may be a virus or a bacteria), defensive medicine, poor perception of negative effects (both adverse effects and ecological impact) and logistical aspects. One significant barrier to the rational process of antimicrobial prescribing is that prescribing decisions are frequently made in an automated mode, omitting some of the critical steps in what it has been called "reflex" prescribing.

Furthermore, antibiotic therapy should be a dynamic process, requiring periodical reassessments. Figure 1 depicts how

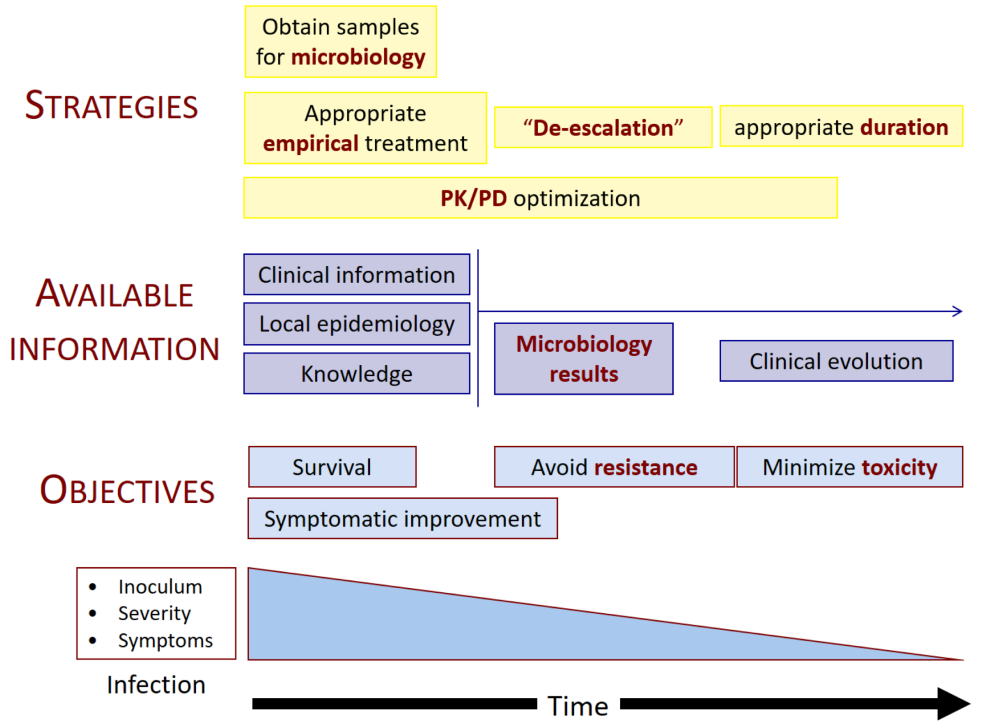

Figure 1 Therapeutic strategies according to the time of infection evolution. Adapted from J. Cobo.

therapeutic strategies should be adapted to the goals and available information, which, indeed, change along the course of the infection.

In 2011, Public Health England outlined a campaign for appropriate antimicrobial use targeting prescribers ("Antimicrobial stewardship: Start smart - then focus") that included several evidence-based recommendations on antibiotic prescribing[3].

Antimicrobial stewardship programs (ASP) are institutional initiatives that aim to optimize antimicrobial prescribing in order to improve patient outcomes and to decrease antibiotic associated adverse effects, including their ecological impact using several strategies[4,5]. Since antibiotic prescribers are the workforce to achieve better antimicrobial use, educational activities targetting prescribers are among the most valuable resources of ASP.

In 2015, Hospital Universitario La Paz (Madrid, Spain) and Hospital Clínico Universitario "Lozano Blesa" (Zaragoza, Spain) ASPs launched a campaign to increase awareness of the main principles of antibiotic use among prescribers based on the Public Health England key messages. The campaing consisted of several vintage-looking posters, inspired in the golden antibiotic era (1940's-1950's) because if antimicrobials had been tought to be used more appropriately, currently antimicrobial resistance use would eventually be a less relevant problem. Every poster contained a key-message to foster appropriate antimicrobial use. Posters can be accessed at http://www. pantuas.com/usoantibioticos/. Overall, the posters conform a decalogue sharing a motto "Not less, not more. Your choice!" emphasizing at the same time prescriber responsibility and autonomy regarding antimicrobial prescribing (figure 2). This campaing has been adopted by the Spanish Agency of Medicines (AEMPS) as part of the Spanish National Plan against Antimicrobial Resistance.

PRACTICAL DECALOGUE

1. Assess your patient carefully before prescribing antibiotics. Antimicrobials should be avoided when there is no evidence or high likelihood of a bacterial/fungal infection. Thus, it is essential to carefully assess the patient in search of clues of an infectious disease that should be treated with antibiotics. Clinical assessment should ocasionally be complemented with laboratory (e.g. biomarkers such as white blood cell count, C-reactive protein and procalcitonin, lactate…) and imaging test in order to reduce uncertainty. Nevertheless, there are circumstances in which antibiotics should be started despite significant uncertainty, such as in patients with febrile neutropenia and in splenectomized patients with fever.

2. In severe infections, start FAST. The prompt initiation of effective antibiotic treatment has a high impact on morbidity and mortality in severe infections.The severity of an infection can be defined either by the degree of

Figure 2 Not less, not more. Your choice! Poster of Antimicrobial Stewardship Program campaing adopted by Spanish Agency of Medicines (AEMPS) as part of the Spanish National Plan against Antimicrobial Resistance.

systemic involvement (sepsis, septic shock) or by its possible consequences/sequelae. In these situations, it is advisable to start the antibiotic as soon as possible, preferably within the first hour of diagnosis.

3. Choose empiric therapy considering local epidemiology and patients' individual factors. When choosing empirical antimicrobial therapy, prescriber needs to be systematic in order to anticipate the most likely etiological agents, their susceptibility patter and, finally the best antibiotic choice. In a didactic way, it can be summed up by the acronym **SAFEx**: **S**yndrome (infectious syndrome or site of infection), **A**cquisition (community, nosocomial or healthcare-associated), individual **F**actors (risk factors for multidrug-resistant microorganisms, colonization or previous infection), local **E**pidemiology (local pathogen prevalence and resistance profiles) and e**X**tra factors (allergies, comorbidities, immunodepression and drugs interactions). Local antibiotic treatment guidelines are of great help to choose empirical antimicrobial therapy since they already consider many of these factors in a wide variety of syndromes and circumstances.

4. Dosing matters, too. Antimicrobial dose optimization needs considering several factors such as those that have just mentioned in the former paragraph as well as the pharmacokinetic and pharmacodynamic properties of the antibiotic to be used.

PK/PD models can be used to predict clinical and bacteriological efficacy and to help identify the most suitable dosage. For instance, in time-dependent antibiotics, like beta-lactams, the bactericidal activity correlates with the percentage of time that the antimicrobial concentration is maintained above the minimum inhibitory concentration (MIC). However, fluoroquinolones and aminoglycosides are concentration-dependent drugs, being the peak concentration and area under the curve predictors of bactericidal effect.

Patients with renal failure might need dose adjustement of several antibiotics which have significant renal clearance. Of note, first dose should not be adjusted since it needs to fill the drug distribution volumen. In the case of antibiotics with a narrow therapeutic range such as vancomycin or aminoglycosides, it may be necessary to determine plasma levels.

5. Get the bug. Obtain samples for microbiological diagnosis before starting antibiotic treatment. Correct sampling of specimens for culture as well as its processing are essential to achieve an etiological diagnosis. Knowing the causative microorganism and its antibiotic susceptibility reduces diagnostic uncertainty and facilitates targeted therapy.

To increase the sensitivity of microbiologic diagnosis, samples shoud be obtained prior to commencing antibiotic, when possible. Nevertheless, do not delay treatment in patients with sepsis or life-threatening infections.

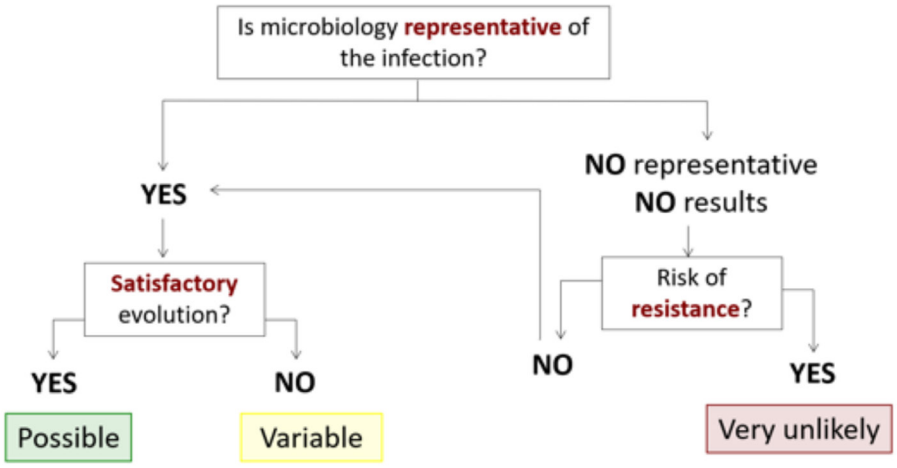

Figure 3 | **Algorithm for de-escalation antimicrobial therapy.**

6. Document in the chart your antibiotic plan: indication and expected duration. Documenting the antibiotic plan in the chart is among the most widely accepted quality indicators for antimicrobial prescribing[6,7]. In addition to helping other healthcare professionals to assist the patient, documenting the antibiotic plan works as a final check in the process of antibiotic prescribing. Prescriber can detect errors in this step of the prescribing process. Documenting the presumed duration of antimicrobial therapy serves as an anchor (heuristics) to guide therapy.

7. Reassess (and adjust) antibiotic therapy periodically. As antibiotic therapy is a dynamic process, it should be reassessed periodically. 48-72 hours after antibiotics have been started, microbiology results frequently become available. Moreover, the clinical course may provide further diagnostic information as well as more clues on the duration of therapy. Reassessing antimicrobial therapy each 48-72 hours facilitates targeted therapy and discontinuation of antibiotics when the evidence of infection is absent.

8. Target antimicrobial therapy when possible. Targeted therapy aims to treat the causative pathogenes, maximizing efficacy and minimizing antibiotic pressure and thus, ecological damage in the form of antibiotic resistance. As a rule of thumb, targeted therapy consists of chosing the antimicrobial with the highest efficacy and the lowest spectrum. Targetting antimicrobial therapy or streamlining is more easily achievable when a strong etiological diagnosis is available.

Nevertheless, streamlining or de-esacalating antimicrobial therapy is not always straightforward. A management algorithm, such as the one depicted by figure 3 can be of help. The most favorable scenario for de-escalation occurs when the microbiological sample is representative of the infection and the clinical response is favorable. In all other circumstances a more thorough approach is necessary.

9. Switch to po (oral route) when possible. Sequential antibiotic therapy (SAT) refers to the conversion of intravenous to oral treatment using an agent from the same or another antibiotic class. Several studies have demonstrated its advantages (safety, convenience and cost-saving). Nevertheless not all infections are suitable for oral antimicrobial therapy. Despite more and more syndromes are being progresively considered good candidates for SAT, there are still a number of infections that are still not, such as endocarditis, primary bacteremia (or endovascular focus), central nervous system infections, acute osteomyelitis, and non-drained visceral abscesses.

In those infectious syndromes in which it has been proven to be effective and safe, SAT should be considered when there the patient is clinically stable (absence of fever in the last 48-72 hours, clinical improvement, and tendency towards normalization of laboratory parameters), there is adequate oral intake and gastrointestinal absorption and adequate antibiotic bioavailability[8].

10. Don't go overtime with antibiotic duration. The duration of the antibiotic treatment should be the minimum that, adapted to the circumstances of each patient, warrants its cure with a minimum rate of recurrence. Too short a course of therapy risks treatment failure, whereas too long a course of therapy carries potential risks for the individual patient and to other patients through the emergence of resistant microorganisms. This requires individualization.

The standard guidelines for therapy often provide a range of appropriate durations, but optimal duration in many situa-

tions is uncertain. More and more evidence is available from clinical trials that shorter courses are as effective as prolonged courses for certain infections[9,10].

Nevertheless, very frequently infections are treated too long since antibiotics provide a false sense of security and the negative consequences derived from their use often go unnoticed or are undervalued. It is essential to increase awareness of the relevance of optimizing the duration of antimicrobial therapy, as well as to change duration framing, and to individualize.

CONCLUSIONS

We have herein summarized the key principles of antimicrobial prescribing that, if correctly applied, should contribute to obtain the best possible outcomes from antimicrobial therapy, minimizing the emergence of resistance, preserving antibiotics as a societal common. These principles should be applied by prescribers, a huge and heterogeneous number of physicians that are part of a complex healthcare system. As knowing does not equal acting, it is relevant to act on all those factors negatively influencing prescribing. Antimicrobial stewardship programs and all other institutional efforts are necessary to achieve this goal.

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Usefulness of Hospital at Home in nosocomial infections: advantages and limitations

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ABSTRACT

Hospital at Home units allows ambulatory treatment and monitoring of complex and serious infections. Nosocomial infections produce an extension of the stay in hospital often specifying long intravenous treatments without any effective oral alternatives. Daily dosing of antimicrobial are easier to administer at home. The use of portable programmable pump infusion and elastomeric devices allow efficient and safe infusions for most antimicrobials at home. Some antibiotics against multidrug-resistant organisms of recent introduction have a suitable profile for outpatient intravenous treatment.

Key words: Hospital at Home, OPAT, nosocomial infections

Utilidad de la Hospitalización a Domicilio en las infecciones nosocomiales: ventajas y limitaciones

RESUMEN

Las unidades de Hospitalización a Domicilio permiten el tratamiento y control ambulatorio de infecciones graves y complejas. Las infecciones nosocomiales suponen una prolongación de la estancia hospitalaria precisando con frecuencia largos tratamientos intravenosos sin alternativa eficaz oral. Los antimicrobianos más sencillos de administrar en domicilio son aquellos con dosis única diaria. La utilización de bombas programables portátiles de infusión y de dispositivos elastoméricos permite infundir con eficacia y seguridad la mayoría de antimicrobianos. Algunos de los antibióticos frente a microorganismos multirresistentes de reciente introducción tienen un perfil muy adecuado para el tratamiento intravenoso ambulatorio.

Palabras clave: Hospitalización a Domicilio, TADE, infección nosocomial

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HOSPITAL AT HOME

Hospital at Home (HaH) is a care modality that allows the care, at home, of patients with acute processes or decompensation of their chronic pathology when they require complex care and treatment suitable to inhospital supervision. If not for this service, these patients should have to remain hospitalized[1].

In recent years a growing number of relevant articles have been published which have increased the level of evidence displaying the advantages of HaH. Compared with conventional hospitalization, we can clearly say that HaH obtains clinical results not inferior to those of the hospital and that it is indeed a safe alternative for suitably selected patients[2].

In a meta-analysis study conducted by Caplan on 62 randomized clinical trials in HaH, it was concluded that clinical efficacy and safety are equivalent to those of patients admitted to a hospital facility. Of the 34 studies in which a cost study was carried out, 32 showed lower costs in HaH, with an estimated average saving of 26.5%. Significant reductions in mortality and re-entry rates were also found. In 22 trials, the satisfaction of patients and caregivers treated at home was analysed, being higher in HaH in 21 of them. No appreciable changes were found regarding the caregiver's overload[3].

Despite these beneficial aspects, the HaH faces a number of constraints stemming both from its insufficient development and virtually no planning. The diversity of care models is striking. In some cases, the HaH units deal with processes that could be performed by primary care teams or other levels of care. This heterogeneity of models hinders the generalization of HaH and its correct evaluation in Spain and its extension to other European countries.

Its implantation in Spain is irregular. According to recently reported data[4] by the Spanish Society for Home Hospitalization (SEHAD), only one out of every 7 acute hospitals in Spain has a HaH unit and only 48% of those units offer

coverage to all of their reference population. The proportion of hospital beds is 2.3 / 103 inhabitants, while the available places of HaH are 0.08 / 103 inhabitants. That is for every 30-hospital beds, there is only one square of HaH. Regarding the overall hospitalization episodes in Spain in 2013 (3,979,900), only 2% were treated in HaH. The situation is worse in other European countries where this care alternative is not even implemented.

HaH is particularly effective in the management of some problems that pose a growing threat to hospital sustainability, such as nosocomial infections or complex chronic patients with frequent hospital admissions. It is a flexible service with the capacity to adapt to the needs of each centre. There are several crucial factors involved in the success of a HaH unit: having an expert team and sufficient means to perform complex care at home and appropriate patient selection[5].

Table 1 **Stability after reconstitution of different antimicrobial agents that required more than once a day dosing.**

ANTIBIOTIC	CONCENTRATION	5º C	25º C
Ampicillin	10-30 mg/mL	48 h	8-24 h
Amoxicillin/clavulanate	5-20 mg/mL	8 h	4 h
Cloxacillin	20 mg/mL	21 d	24 h
Cefepime	1-40 mg/mL	7 d	12-24 h
Ceftaroline*	12 mg/mL	24 h	6 h
Ceftazidime	1-40 mg/mL	21 d	12-48 h
Ceftazidime/avibactam*	40/10 mg/mL	24 h	12 h
Ceftolozane/tazobactam*	10/5 mg/mL	7 d	24 h
Doripenem	5-10 mg/mL	7 d	4-24 h
Meropenem	1-20 mg/mL	2448 h	6 h
Piperacillin/tazobactam	100-150 mg/mL	48 h	24 h
Vancomycin	5 mg/mL	7 d	24 h

*** Recently introduced. Limited experience. h = hours; d = days**

OUTPATIENT PARENTERAL ANTIMICROBIAL THERAPY

Outpatient parenteral antimicrobial therapy (OPAT) consists on administering through intravenous, intramuscular or subcutaneous routes two or more doses of an antimicrobial on different days, to non-hospitalized patients, ie not staying overnight in the hospital[6]. The OPAT includes administration anywhere, as long as the patient is not admitted to a hospital. Thus, apart from the home, antimicrobials can be administered on an outpatient whose care is taking place in day hospitals, outpatient clinics, emergency services, primary care centres, nursing homes or infusion centres[7].

In Spain OPAT is usually performed by HaH units[8,9]. These are healthcare structures dependent on the hospitals from which they draw both their human and material resources[1]. It is very important that the medical and nursing staff that integrate these units have a specialized training that allows them to provide comprehensive care to the infected patient. OPAT should not be an isolated procedure and must be inserted in a set of diagnostic, therapeutic, preventive and health education activities[8]. In other countries, especially in the United States, due to the high costs of medical visits, OPAT activity is fundamentally based on nursing. This less medicalized care scheme has fewer guarantees, especially in complex[10] or pluri-pathological patients, than the one based on HaH units.

Selection process for OPAT. The safety and efficacy of OPAT depends on the correct selection of the patient and its infectious process, the prescribed antimicrobial agents, the venous access route and the infusion devices and modalities. Prior to the decision on each of these aspects should be clearly established the need to use the intravenous route to treat the infectious process.

Patient selection. Not all patients are candidates to be treated on an outpatient basis. From the clinical point of view, a diagnosis of certainty, clinical stability and absence of comorbidity with intrinsic indication of hospital admission are required. Requests for patients residing outside the geographical coverage area of the HaH unit should be rejected and also if adequate human, material and organizational resources are not available and appropriate to each case needs. The existence of a trained caregiver, the hygienic conditions of the home and the availability of telephone communication are necessary requirements to guarantee the quality and safety of health care.

Exclusion criteria for OPAT generally include active addiction to intravenous drugs, acute psychosis, suicidal ideation, indigence, habitual lack of light and running water, and inability to collaborate when necessary or to understand the risks of the procedure.

Selection of infectious process. The commercialization of new antimicrobials with a better safety profile and more convenient dosing[11,12] and the existence of increasingly versatile infusion devices allow us to affirm that almost any infectious process is susceptible to be treated in HaH units. Limitations are determined by patient conditions and the availability of resources.

In addition, the number of cases attended to at the home without a previous period of hospitalization is increasing[13]. Despite the positive effect of this strategy on saving hospital stays, infections with high risk of serious complications should be admitted to the hospital as a step prior to home treatment. This category includes, among others, endocarditis[14,15], meningitis and severe sepsis of any aetiology.

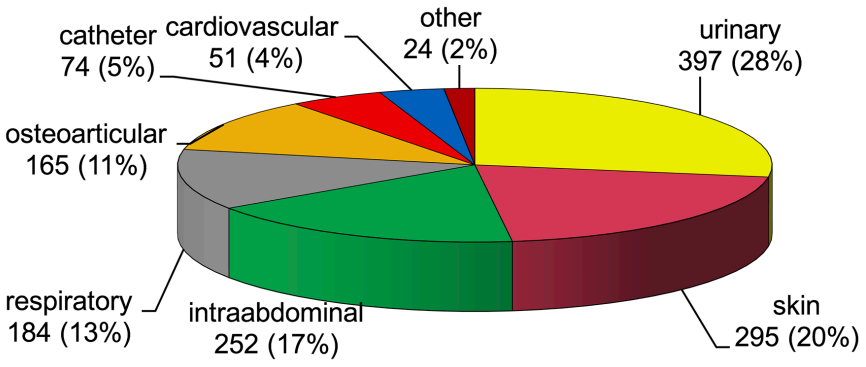

Figure 1 Type of nosocomial infections treated in Hospital at Home Units of Spain. Data from the TADE Registry.

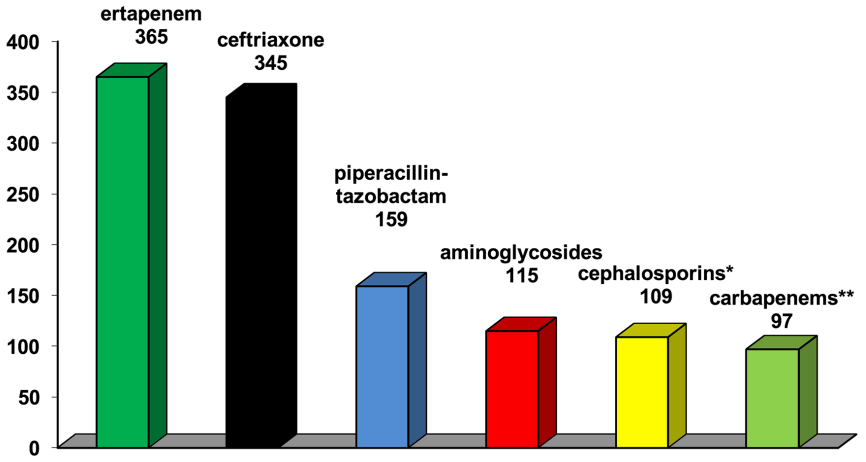

Figure 2 Antimicrobials mainly used in nosocomial infections by the HaH units in Spain. Data from the TADE Registry.

* Ceftriaxone excluded
** Ertapenem excluded

Antimicrobial selection. In the selection of the most appropriate antimicrobial for OPAT, it is necessary to consider the type of infection, the drug physicochemical characteristics, dosage, safety profile, infusion time, type of venous access, patient preferences and, in the case of needing their collaboration, the capacity of understanding and the ability of the caregiver.

Classically it has been considered as an ideal antibiotic if it combines a good safety profile, activity spectrum that allows the use in monotherapy, administration in single daily dose, brief time infusion, low cost and the possibility of intramuscular administration[16]. Drugs that require more than one daily dose and are stable at room temperature for 24 hours once diluted (table 1) can be administered with programmable electronic devices[17]. When they are not stable, self-administration can be used with pre-filled and refrigerated elastomeric pumps[18], or by gravity.

Venous access selection. The main factors influencing the choice of catheter and the insertion site are the characteristics of the drug, the duration of treatment and the patient's preferences. In general, thick-gauge (central or peripheral catheter) veins should be channelled when drugs with high irritant potential (ampicillin, cloxacillin, and doxycycline) are administered, when extravasation can lead to tissue necrosis (acyclovir) and prolonged treatments. Whenever possible it must be taken into consideration the patient's opinion for catheter location.

Selecting the mode and infusion device. At home, four infusion modalities are used: direct intravenous, gravity, infusion with electronic pumps, and infusion with elastomeric pumps, each option with its advantages and limitations.

Indications. Early OPAT experiences focused on infections requiring long-term parenteral antibiotic treatment and which in turn did not represent imminent vital risk. Examples of these indications were osteomyelitis[19] and septic arthritis, soft tissue infections, respiratory infections in patients with cystic fibrosis, etc. The spectrum of infections for OPAT was progressively expanded by its safety and favourable clinical results[20, 21].

The emergence of more effective, safe and long-lasting antibiotics and the availability of improved infusion equipment have allowed this expansion. At present, practically any infection can be treated in the outpatient setting if the patient's clinical conditions allow it and if there are enough qualified assistance teams. New antimicrobials such as ceftolozano/tazobactam, dalbavancin or tedizolid are very suitable for OPAT.

OPAT IN NOSOCOMIAL INFECTIONS

There is little information about the safety and effectiveness of OPAT in infections acquired in acute care hospitals. Some studies have analysed it in infections caused by multidrug resistant microorganism, irrespective of the place of acquisition. In a prospective observational study carried out in a

Table 2 **Percentage of multi-resistant microorganisms from nosocomial vs. community acquired infections treated in HaH units in Spain. Data from the TADE Registry.**

MICROORGANISM	NOSOCOMIAL (n = 1442)	COMMUNITY (n = 6023)	p value
Staphylococcus MR	112/199 (56.2%)	112/349 (32%)	< 0.001
S. aureus MR	39/97 (40.2%)	77/248 (31%)	0.10
S. coagulase negative MR	73/102 (71.5%)	35/101 (34.6%)	< 0.001
Eschericha coli ESBL	146/283 (51.6%)	417/1339 (31.1%)	< 0.001
Klebsiella pneumoniae ESBL	98/150 (65.3%)	124/258 (48%)	< 0.001

HaH: Hospital at Home; MR = methicillin-resistant; ESBL: extended spectrum beta-lactamase

Spanish Hospital at Home Unit during 2008-2012 period, 433 infections caused by multidrug resistant bacteria were treated intravenously at home[22]. The antibiotic drugs were administered either by caretakers or were self-administered by patients with elastomeric devices. 79% of these infections were health-associated without distinction between acute hospital or other place acquisition. Hospital readmissions were uncommon, but there were increased readmissions in the case of enterococal and/or healthcare-associated infections.

We have used the episodes included during the first five years (2011-2016) of the TADE Registry in which we collected the OPAT treatments performed at more than thirty Spanish HaH units, in order to analyse the characteristics of nosocomial acquisition infections by comparing them with community acquired.

Of the 9,314 OPAT episodes included, 1,463 (16%) were acquired in an acute hospital (group N) and 7,063 (76%) in the community (group C). The mean/average age of the N group (67.6; range 11-100) was not different from that of the C group (66.7; range 2-107), with males predominating in both groups (64.1% vs 55.7%). The Charlson index was significantly higher in the N group (3.2 $\pm$ 2.3 vs 2.3 $\pm$ 2.2).

The most frequent sites of nosocomial infection were urinary (28%), cutaneous (20%) and intraabdominal (17%) (figure 1), while in the community they were urinary (35%), respiratory and cutaneous (13%). In group N, 74 episodes (5%) of intravascular catheter-associated infection were treated.

The most frequent causative microorganisms in the N group were *Escherichia coli* (19.3%), *Pseudomonas* (14.8%), *Staphylococcus* (13.6%) and *Klebsiella* (11%), while in C they were *E. coli* (22.2%), *Pseudomonas* (14.2%), *Staphylococcus* (5.7%) and *Streptococcus* (5.4%). The percentage of methicillin-resistant *Staphylococcus* was greater in group N (56.2% vs 32%). The percentage of ESBL-bearing Enterobacteriaceae was *Escherichia* (51.6% vs 31%) and *Klebsiella* (60.8% vs 42.3%) (table 2).

In figure 2 we show the antimicrobials most used in group N (figure 2). Electronic infusion pumps (27.6%) or elastomeric devices (22%) had to be used in a similar percentage in both groups. Self-administration was used in 17% of cases without differences between groups.

The duration of OPAT was similar in both groups (9.4 vs 9.8 days) with previous stay in conventional upper hospitalization in N (15 vs 5.5 days). A total of 117 patients (8.1%) from the N group and 263 (4.3%) from the C group were required for non-scheduled rehospitalization, and 13 patients in the N group (0.9%) and 87 (1.4%) in the C died.

These results suggest that despite the greater comorbidity of patients and the presence of more multi-resistant microorganisms, HaH units are an effective and safe care tool for the treatment of nosocomial infections.

The general advantages advocated for HaH assistance are especially evident when used for OPAT. In a recent economic study carried out in three Spanish centres[23] the economic savings obtained with the use of OPAT in HaH compared to maintenance in conventional hospitalization was higher than 80% for each stay. This saving is much higher than that reported for other non-infectious HaH indications (ie, chronic diseases, palliative care).

The hospital gains an additional advantage by not needing to block beds or use other measures to avoid the transmission of nosocomial infection that is frequently produced by multi-resistant microorganisms that require isolation.

CONCLUSIONS

HaH is an effective and safe alternative in the treatment of nosocomial infections through OPAT. It also has both clinical advantages and perceived quality for the patient as well as costs and avoiding problems created by isolation for the hospital.

At present the type of antimicrobial is not a limitation for the realization of OPAT, being able to be administered in the great majority, in ambulatory form. The participation of the patient and their caregivers in the infusion process is a booming practice that facilitates the administration of complex treatments.

The main limitations to the practice of OPAT are restricted to the clinical instability of the patient and the absence of adequate social conditions in the home.

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Non-antibiotic treatment for infectious diseases

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ABSTRACT

The abuse and uncontrolled use of antibiotics has resulted in the emergence and spread of resistant bacteria. The utility of conventional antibiotics for the treatment of bacterial infections has become increasingly strained due to increased rates of resistance coupled with reduced rates of development of new agents. As a result, multidrug-resistant, extensively drug-resistant, and pan-drug-resistant bacterial strains are now frequently encountered. This has led to fears of a "post-antibiotic era" in which many bacterial infections could be untreatable. Alternative non-antibiotic treatment strategies need to be explored to ensure that a robust pipeline of effective therapies is available to clinicians. The new therapeutic approaches for bacterial infections (beyond antibiotics) may provide a way to extend the usefulness of current antibiotics in an era of multidrug-resistant (MDR) bacterial infections.

Tratamiento no antibiótico de las enfermedades infecciosas

RESUMEN

La utilidad de los antibióticos convencionales en el tratamiento de las infecciones bacterianas se ha visto comprometida debido a las elevadas tasas de resistencia junto con la reducción en el número de nuevos agentes en desarrollo. Como resultado, ahora es frecuente encontrar cepas bacterianas multirresistentes, extensamente resistentes o panrresistentes. Esto nos transporta a una era post-antibiótica en la cual muchas infecciones bacterianas podrían ser intratables. Se necesitan explorar estrategias de tratamiento alternativas a los antibióticos que aseguren un "pipeline" robusto de terapias efectivas que lleguen a estar disponibles para los clínicos. De esta forma, las nuevas estrategias terapéuticas (más allá de los antibióticos) aportarán una vía para extender la utilidad de los antibióticos actuales en una era de infecciones por bacterias multirresistentes (MDR).

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INTRODUCTION

It is undeniable that antibiotics have had an enormous impact on global human health by drastically reducing infection-associated mortality. Nonetheless, the abuse and uncontrolled use of antibiotics has resulted in the emergence and spread of resistant bacteria. The utility of conventional antibiotics for the treatment of bacterial infections has become increasingly strained due to increased rates of resistance coupled with reduced rates of development of new agents. As a result, multidrug-resistant, extensively drug-resistant, and pan-drug-resistant bacterial strains are now frequently encountered. This has led to fears of a "post-antibiotic era" in which many bacterial infections could be untreatable. Whilst resistance to antibiotics has escalated steadily, the number of new antimicrobial drugs approved, especially those with novel modes of action, continues to decline. Among the vast number of Gram-positive and Gram-negative bacteria, the 'ESKAPE' group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* species) represent the most common antibiotic-resistance pathogens.

Given the rise of antibacterial resistance and the challenges of common antibacterial agent discovery and development that have led to a very small pipeline of new therapies, it would be prudent to consider the potential role of non-conventional approaches[1]. Alternative non-antibiotic treatment strategies need to be explored to ensure that a robust pipeline of effective therapies is available to clinicians[2].

Table 1 Agents that inhibit toxins (effector proteins) and secretion systems (chemical inhibitors and antibodies)

Name of product	Type	Target	Bacterium	Development phase
Shigamab	Monoclonal antibodies	Stx-1, Stx-2	*E. coli*	Phase 2 clinical trial
Raxibacumab	Monoclonal antibody	Cellular receptor anthrax toxin	*B. anthracis*	Animal model
Bezlotoxumab	Monoclonal antibody	Toxin B	*C. difficile*	Completed phase 3 clinical trial
MEDI4893	Monoclonal antibody	α- hemolysin	*S. aureus*	Phase 2 clinical trial
Compounds 1-9	Small molecules	Type 2 secretion systems	*P. aeruginosa, B. pseudomallei*	Preclinical (inhibition of bacterial secretion)
Compounds 7086, 7832, 7812	Small molecules	Type 3 secretion systems	*Yersinia pestis*	Preclinical (efficacy in cell culture)
Salicylidene acylhydrazides	Small molecules	Type 3 secretion systems	*Salmonella, Shigella, Chlamydia, Yersinia, Pseudomonas*	Preclinical (efficacy in mice)
CHIR-1	Small molecules	Type 4 secretion systems	*H. pylori*	Preclinical (efficacy in mice)

Adapted from reference 4 (Hauser AR, et al. Clin Infect Dis 2016; 63: 89–95).

In this review, we explore a range of therapeutic strategies that could be employed in conjunction with antibiotics and may help to prolong the life span of these life-saving drugs. In this article, we highlight some of the recent developments in this area, such as the targeting of bacterial virulence factors, utilization of bacteriophages to kill bacteria, vaccines to prevent healthcare-associated infections (HAI) and manipulation of the microbiome to combat infections. Thus, the new therapeutic approaches for bacterial infections (beyond antibiotics) may provide a way to extend the usefulness of current antibiotics in an era of multidrug-resistant (MDR) bacterial infections.

ANTI-VIRULENCE STRATEGIES

Bacterial pathogens produce virulence factors, molecules that allow them to resist clearance by the host, to invade and gain access to deeper tissues, and to damage host cells. Several innovative alternatives under development interact with virulence factors, making it easier for the immune system to fight them[3]:

Inhibition of toxins and secretion systems. Agents developed can be chemical inhibitors or antibodies (table 1). **1**) Most gram-negative bacteria release toxins via their type III secretion system (T3SS), a complex multiprotein, needle-like apparatuses to inject toxins directly into human cells. T3SS' inhibitors may be active against multiple different bacteria (e.g. KB001 (KaloBios), a pegylated, humanized anti-PcrV antibody Fab' fragment, was safe and showed a trend toward decreasing the development of ventilator-associated pneumonia in *P. aeruginosa* colonised patients; **2**) MEDI3902 (AstraZeneca), a chimeric bispecific monoclonal antibody that recognizes both PcrV and the polysaccharide Psl located on the surface of *P. aeruginosa;* **3)** Raxibacumab (GlaxoSmithKline), a fully humanized immunoglobulin G1 (IgG1) monoclonal antibody that prevents anthrax toxin binding to its host cell receptor, is now recommended for the adjunctive (along with conventional antibiotics) treatment of inhalational anthrax[4], **4)** Antibodies H3H, F3A and F4H suppress the catalytic domain of neurotoxin serotype A in *Clostridium botulinum*).

Targeting biofilms and adherence. Novel methods are being developed that are designed to prevent biofilm formation and to disaggregate biofilms once formed; however, to date these newer strategies have not reached the clinical testing stage[5], although previous modifications of inert substances have been described. **1**) Catheters coated with the zwitterionic polymeric sulfobetaine had reduced amounts of both *S. aureus* and *Escherichia coli* adhesion, and animals treated with these catheters experienced fewer infections. **2**) c-di-GMP, a small signaling molecule, has also been a recent target to prevent infections by *biofilm*-forming pathogens because it regulates the switch that allows planktonically grown bacteria to form biofilms. **3**) Inhibitors of the *pili* biosynthesis (pilicides) reduce the adhesion of bacteria to the epithelium and consequently reduce *biofilm* formation; uropathogenic *E. coli* (UPEC), which causes urinary tract infections, uses a lectin-type fimbriae adhesin to attach to epithelial cells. Small molecules have been developed that interfere with the binding of the fimbriae to sugar moieties on epithelial cell surfaces. For example, ZFH-04269 molecule caused a 1000-fold reduction in the number of UPEC bacteria in the bladders of chronically infected mice.

Targeting signaling and regulation. Quorum-sensing (QS) is a cell density–dependent communication system that utilizes low-molecular-weight signaling molecules (autoinducers) to regulate virulence in many bacterial pathogens. In general, gram-negative species use

N-acylhomoserine lactones (AHLs) or related compounds, and gram-positive species use ribosomally produced autoinducing peptides for QS. M64, a phenoxy derivative of a substituted benzamide moiety with endocyclic aromatic amines, follows the former strategy by inhibiting MvfR, a transcriptional regulator of the 4-hydroxy-2-alkylquinoline QS system of *P. aeruginosa*. Interference with QS of bacteria via 5'-methylthio-DADMe-ImmucillinAs, 5'-ethylthio-DADMe-ImmucillinAs and 5'-butylthio-DADMe-ImmucillinAs, which inhibit the 5'-Methylthioadenosine nucleosidase (MTAN), an enzyme involved in QS of *E. coli* and *Vibrium cholerae*, reducing the biosynthesis of autoinducers AI-1 and AI-2 (signaling molecules), the ability to form biofilms, reducing the infection capacity and the resistance to antibiotics[6].

These antivirulence strategies have as main advantage the fact of being specific to virulence factors that only exists in pathogenic bacteria, so they do not affect the commensal flora in the host. In addition, these antibacterial approaches can be administered either topically or systemically. Finally, combining antivirulence compounds with conventional antibiotics may provide synergistic enhancement of efficacy.

BACTERIOPHAGES AND PHAGE THERAPY

Bacteriophages, or phages, are viruses that only infect bacterial cells. They are biological entities known for over a century. Phage particles represent the most abundant biological entities on the planet, and total phage abundance in the biosphere has been estimated at 1030, or more. However, only now a special interest on phages has been rediscovered, as a potential alternative or complement to current antimicrobial chemotherapy due to their highly specific and unique properties to fight bacterial strains resistant to conventional antimicrobial drugs. Phages are biological entities completely devoid of any metabolic machinery, and thus are obligate intracellular parasites that require a bacterium to replicate themselves, through their genetic material, by taking over the biochemical machinery of the bacterial cells. Bacteriophage therapy, although not new, makes use of strictly lytic phage particles as an alternative, or a complement, in the antimicrobial treatment of bacterial infections. It is being rediscovered as a safe method, because these biological entities devoid of any metabolic machinery do not possess any affinity whatsoever to eukaryotic cells[6].

Most phages discovered until the present day are specialized in interacting with bacteria that express specific receptors and, if the bacterium does not show at the surface a specific receptor for a particular bacteriophage, then the phage becomes naturally (and highly) specific for a given bacterial host. It is estimated that for every bacterial cell, there are ten different bacteriophages, some of which are highly specific for their host – meaning that they recognize only one type of receptor (monophage), while others have a broader host range and recognize more than one type of receptor (polyphage). Phage therapy has been applied over the past few decades to the treatment of bacterial infections, in countries where research and development centres were built specifically for bacteriophages aiming at developing phage therapy. Bacteriophages were used for antibacterial therapy in Russia and Eastern Europe before the advent of antibiotics, and recent dramatic increases in infections with MDR bacterial strains are driving new interest in this approach. The studies conducted in these research centres produced remarkable clinical results. However, and despite the immense potential of bacteriophages for eradicating infections caused by bacterial-resistant strains, up to now only a few clinical trials have been performed in human beings and are accepted by public health authorities.

Phages offer several important advantages over traditional antibiotics. They are specific for bacteria and even particular strains and species of bacteria, they do not infect human cells, and they have little or no effect on normal microbial flora[4]. Limitations include the development of bacterial resistance and immune responses, difficulties in purification from bacterial endo- and exotoxins, and formulation and stability issues in systemic delivery. For these reasons, most studies have been done with topical, gastrointestinal, or pulmonary deliveries. As mentioned, phages have the advantage of being exquisitely specific, but this is also a disadvantage, as cocktails of multiple phages are required to target multiple species and even most strains within a species. Nevertheless, several phage cocktails have exhibited efficacy in animal infection models. Although not a complete litany of their disadvantages, of primary concern is the integration of phage DNA into the bacterial genome, the failure of bacteriophage therapy due to restrictive specificity, and the development of bacterial resistance based on alteration of the bacterial cell surface receptor. A cocktail containing several different phages, especially when used in conjunction with a traditional antibiotic may circumvent these disadvantages. Alternatively, using bacteriophage components (e.g., virolysin, antimicrobial peptides, etc.) may avoid many, if not most, of these pitfalls, serving as a significant source of potent new antimicrobials. Furthermore, using a modified phage coat to display an antigenic peptide, in conjunction with its natural bacterial targeting specificity, may potentially provoke the host immune response at the site of infection[2].

Recent technological advances in this field open the door to the possibility of customizing bacteriophages and improve their characteristics, particularly: (i) expand the ability of bacteriophages to penetrate bacterial biofilms; (ii) enlarge their potency and effectiveness; (iii) adapt the spectrum of activities of bacteriophages to infections caused by numerous bacterial species and strains; and (iv) make them more stable and specific. Strategies to improve phage therapy have involved engineering phages to increase their infectivity and host range and purifying individual phage components to target bacteria[7].

VACCINES

Over the past few years, the prophylaxis of multidrug-resistant pathogen infections through the use of vaccines and passive immunization has become of great interest

due the high economic and ecological cost of antibiotic treatment, as well as the lack of therapeutic targets for the development of new antimicrobials[8]. Its application in high-risk patients will both prevent infections and reduce the use of antimicrobials and the consequent development of resistance. The lack of appropriate predictive models and the selection of high-risk target population are the main challenges in its development.

Among the pathogens considered as urgent threats to public health, *Clostridium difficile* is the one that has achieved greater progress. Different vaccines based on purified and inactivated toxins A and B are in advanced stages of development, showing to be safe and immunogenic[9]. Different surface antigens are also being studied for its incorporation in future vaccines in order to prevent host colonization and cross-transmission.

S. aureus is known for its wide range of virulence factors and host immune evasion mechanisms. Several vaccines (StaphVAX or V710) have failed in their development for several reasons including the complexity of pathogenic mechanisms, extensive antigenic variability, biofilm formation capacity or immune evasion mechanisms[10]. There is currently a developing program for an antigenic vaccine (SA4Ag), which has shown rapid immunogenicity in early studies, being under investigation in a phase 2b study.

Among the Gram-negative bacteria, the vaccines against *P. aeruginosa* have presented a greater development, having already been concluded a phase 3 study (IC43). The variability of *K. pneumoniae* and *E. coli* capsular polysaccharides limit their potential as vaccine targets, and the extracellular vesicles are currently under investigation as potential immunogenic agents. Studies with *Acinetobacter spp.* still in early stages, focusing on the selection of specific antigens.

There are currently two vaccines in phase 2 to prevent vulvovaginal candidiasis, but no specific vaccines have yet been developed to treat invasive fungal infections.

On the other hand, the use of monoclonal antibodies (mAbs)[11] has taken center stage in the last years. *C. difficile*, *S. aureus* and *P. aeruginosa* mAbs are currently in phase 2-3 clinical trials[12], whereas mAbs against *E. coli*, *Klebsiella spp.* and *Acinetobacter spp.* are still in early stages. MAbs do not require adaptive immune response and could be investigated in immunocompromised patients, being of potential useful as therapeutic or prophylactic treatment. Most of them are targeted to toxins and therefore could be considered as antivirulence strategies that can mitigate the disease without promoting antibiotic resistance, but may also require the use of antibiotics to reduce bacterial load.

MICROBIOME MODULATION

Human microbiota is the amount of microorganisms that are found in human body and microbiome is the collection of all their genomes. In a healthy adult colon, (the most investigated body habitat), there are more or less 160 bacterial species (mainly *Bacteroidetes* and *Firmicutes*) which contribute to regulate physiological functions. Disruption of this ecosystem has been associated with many illnesses like diabetes mellitus, cardiovascular diseases, asthma, autism, inflammatory bowel disease (IBD), antibiotics-associated diarrhoea and cancer.

Microbiome usefulness in medicine. At this moment, the most encouraging application of microbiome in medicine is in the sphere of treating recurrent infections caused by *C. difficile*, an anaerobic, esporulating, toxin former, gram-positive bacilli which represents the leading cause of healthcare and antibiotics-associated diarrhoea and pseudomembranous colitis[13].

A. Prebiotics. They are non absorbible polysaccharides (like inulin and fructo-oligosaccharides) that have positive influence in host health, stimulating biodiversity of human gut microbiome. There are studies in which prebiotics have been taken by patients with antibiotics-associated diarrhoea but results about its effectiveness are contradictory[14].

B. Probiotics. They are live microorganisms that, when used at proper concentrations, give benefit to host health, helping to preserve normal microbiome and preventing the growth of pathogenic bacteria[15]. For example, *Saccharomyces boulardii* and *Lactobacillus* species could reduce the incidence of *C. difficile* infection (CDI); *Lactobacillus salivarius* may inhibit the growth of *Listeria monocytogenes*; *Streptococcus mutans* could confer protection against development of dental caries and vaginal applications of *Lactobacillus jensenii* may defend women from infection produced by *Gardnerella vaginalis*, *Candida albicans* and *E. coli*.

C. Faecal microbiota transplantation (FMT): In FMT, faeces from a healthy person are employed in order to restore gut microbiome which is disrupted in a sick patient, suppressing *C. difficile* and other microorganisms overgrowth. This procedure has shown a rate of cure of recurrent CDI around 90%. Results in IBD are less consistent and there are a few case series reports of patients with neurological disorders like multiple sclerosis or Parkinson disease who achieved sustained improvement and patients with autism which symptoms ameliorated by this approach. It may be useful to treat infections caused by drug-resistant bacteria like vancomycin-resistant enterococci or multidrug-resistant *K. pneumoniae*[16], as it has been shown in two patients who had undergone hematopoietic cell transplant, but nowadays, further investigations are needed to make a high quality evidence based recommendation[17].

CONCLUSIONS AND FUTURE VISION

The global burden of antimicrobial resistance is rising and is associated with increased morbidity and mortality in

clinical and community setting. Spread of antibiotic resistance to different environmental niches and development of superbugs have further complicated the effective control strategies. International, national and local approaches have been advised for control and prevention of antimicrobial resistance. Rational use of antimicrobials, regulation on over-the-counter availability of antibiotics, improving hand hygiene and optimizing infection prevention and control are the major recommended approaches. Thorough understanding of resistance mechanism and innovation in new drugs, antibiotic delivery systems, other potential non-antibiotic alternatives and vaccines are needed[18]. A multidisciplinary, collaborative, regulatory approach is demanded for combating antimicrobial resistance. Solutions to antibiotic resistance are not trivial to implement, with consequences affecting everyone. While solutions have been proposed, with some even being launched to address the problem, action taken to date is merely token. Antibiotics remain indispensable in all health systems, and the consequences of a lack of a medically, socially, and economically coordinated effort will be dire. Simple antibiotic stewardship is no longer an option in the face of rising drug resistance. Clinical treatments and practices for infection control must evolve in response to epidemiological trends in MDR bacteria and the development of new treatment strategies. Hopefully, repeated emphasis will promote adoption of new research strategies for infection treatments, including adherence to three criteria: (1) invention of effective new drugs, (2) prevention of resistance, and (3) protection of the natural host microbiome. The best strategy to meet these criteria includes the development of new combination approaches coupled with local and smart delivery technologies.

The extraordinary success of conventional antibiotics led to a focus on development of these agents to the exclusion of other antibacterial strategies[19]. A silver lining in the current dark cloud of antibiotic resistance is that these alternative strategies are again being pursued, although significant challenges remain before they can be widely adopted into clinical practice. Many of these compounds are still in the preclinical phase of development, and a substantial investment in time and resources will be necessary before they significantly impact the ability of physicians to treat patients infected with MDR bacteria. The next step is to establish out which alternatives to antibiotics are most likely to deliver new therapies of clinical use. Experts have found that academic researchers and the pharmaceutical industry have successfully generated a diverse portfolio of potential alternatives-to-antibiotics projects. Results from studies of these approaches are still emerging and these approaches hold promise provided that adequate funding is available for researchers to build capacity and create a preclinical evidence base to enable prioritization and progress of optimized drugs to following crucial phase validation. So, this first wave of new approaches will probably best serve as adjunctive or preventive therapies. Therefore, traditional antibiotics will still be needed. In an assessment of the future impact of alternative technologies on antibiotics markets, ten alternative technologies were identified and analysed for their potential impact on the antibiotics market. Of these, rapid point-of-care diagnostics, vaccines, FMT, and probiotics were considered to have a "high" or "medium" potential impact over a 10-20 year horizon[20]. Therapeutic antibodies, antibiotic biomaterials, bacteriophages, antimicrobial nanoparticles, antimicrobial peptides, and anti-virulence materials were rated as having "low" potential impact. Despite the apparent potential of the most promising alternative technologies to reduce demand of antibiotics, that reduction will likely only happen in limited segments of the antibiotics market or, in case of preventing community acquired infections by vaccination, in a low-price generics market segment. Thus, alternative technologies are not expected to represent any disincentive to antibiotics developers. Therefore, it is unlikely that alternative technologies will displace the need for new classes, and sub-classes, of antibiotics in short and medium-term.

Longer term substantial and sustainable funding will be needed to advance and make use of the wider alternatives-to-antibiotics portfolio. Policy and funding should now be linked. Without sufficient funding we can assume that new treatments to replace or supplement antibiotics will not be available, and the consequences of such a prolonged delay for global health-care systems need to be considered now. If these difficulties can be surmounted, alternatives to antibiotics may become important therapeutic options for bacterial infections.

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Evaluation questionnaire

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1. Regarding the sensitivity of the prognostic scales in sepsis, indicate the true:

A) SIRS is more sensitive than the SOFA in the patients treated in ER
B) The qSOFA is less specific than the SIRS in the patients treated in the ER
C) The false negatives applying the SIRS in the patients of Emergencies are of more than 10%
D) The positive predictive value of SIRS, SOFA and qSOFA exceeds in all cases 20%

2. Regarding the diagnosis of sepsis, considering the last definitions, indicate the correct one:

A) Sepsis was diagnosed when qSOFA ≥2
B) Sepsis is diagnosed for presenting a SOFA ≥2
C) Sepsis is diagnosed as presenting an increase in qSOFA ≥2
D) Sepsis is diagnosed as presenting an increase in SOFA ≥2

3. Regarding the stratification of short-term mortality in the elderly population, indicate the correct one:

A) The SIRS criteria are the ones that best classify the severity of this population
B) qSOFA has shown in this population a great sensitivity
C) Good results are obtained by applying the GYM scale (Glasgow, tachypnea, comorbidity)
D) a and b are correct

4. What is the main mechanism of resistance to ceftazidime in *P. aeruginosa*?

A) Mechanisms mediated by ejection pumps and porins
B) Chromosomic betalactamase hyperproduction - ampC
C) It is always because it acquires extended spectrum beta-lactamases and / or carbapenemases
D) None is true

5. Regarding the hospital epidemiology of *P. aeruginosa*:

A) It is one of the main microorganisms that cause pneumonia related to mechanical ventilation.
B) In recent years has increased the percentage of multiresistant strains
C) The molecular epidemiology of *P. aeruginosa* is characterized by the presence of epidemic clones or high risk clones that could be responsible for the dissemination of multiresistant strains
D) All are true

6. State the correct answer:

A) Ceftolozan-tazobactam shows good activity against strains of multiresistant *P. areruginosa*, but is not active against strains producing carbapenemase
B) Ceftazidime-avibactam has good activity against strains of multiresistant *P. areruginosa*, but is not active against strains producing carbapenemases type metallobetalactamases (MBL)
C) All are correct
D) All are false

7. Which of the following is a risk factor for participation of multiresistant microorganisms in ventilator-associated pneumonia?

A) 3 or more antibiotic cycles in the previous 3 months
B) Acute respiratory distress preceding the development of pneumonia
C) Acute renal failure requiring the use of renal replacement techniques
D) All of the above

8. The decision whether or not to initiate antibiotic treatment in case of suspected nosocomial pneumonia or mechanical ventilation should be based on:

A) Only in clinical criteria
B) In clinical criteria plus the evaluation of procalcitonin
C) In clinical criteria plus the assessment of sTREM-1
D) In clinical criteria plus the assessment of the PCR

9. Empiric antibiotic treatment of nosocomial pneumonia or ventilator-associated pneumonia should be active against:

A) *Staphylococcus aureus* and ESBLs producing *Enterobacteriaceae*
B) *Staphylococcus aureus* and *Pseudomonas aeruginosa*
C) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
D) *Enterobacteriaceae* and *Enterococcus* spp.

10. The prevalence of infection associated with vascular grafts is approximately:

A) > 1%
B) 5%
C) 25%
D) > 50%

11. Coagulase negative staphylococci are the microorganisms that are most frequently involved in the infection associated with pacemakers. The second microorganism in frequency is:

A) *Escherichia coli*
B) *Candida albicans*
C) *Pseudomonas aeruginosa*
D) *Staphylococcus aureus*

12. Which of the following antimicrobials has activity against microorganisms in stationary phase?

A) Amoxicillin
B) Doxycycline
C) Daptomycin
D) Vancomycin

13. Given the suspicion in a patient of catheter-related bacteremia, how would you rule out that there is no infection (without catheter withdrawal) in less than 24 hours?

A) Perform 3 blood cultures
B) Perform two blood cultures by the peripheral route and another by the catheter
C) Perform semi-quantitative cultures of the pericatheter skin and the connection.
D) Request differential blood cultures

14. In a patient infected with HIV and with meningitis, how could cryptococcal meningitis be ruled out in less than 4 hours?

A) Cultivation of the CSF
B) Perform a staining of the CSF with Chinese ink
C) Perform a real-time PCR for *Cryptococcus sp*
D) Perform an immunochromatographic test in urine for *Cryptococcus* sp

15. In a patient admitted to the ICU with pneumonia, how can the presence of MRSA be ruled out in less than 4 hours?

A) By Gram staining of the sputum and observing gram-positive cocci in clusters
B) Perform a real-time PCR to detect the *mec*A gene
C) Perform a real-time PCR to detect the presence of *S. aureus*
D) All of the above are false

16. The following statements regarding resistance problems in complicated intra-abdominal infections are true:

A) Isolates of E. coli producing ESBL accounts for <1%
B) The problem of resistance is particularly acute in the Asia-Pacific region
C) The proportion of ESBL-producing E. coli has reached 40% in 2012 in the Asia-Pacific region according to the SMART study
D) b and c are true

17. The following statements regarding the microorganisms responsible for intra-abdominal infection are true:

A) *Pseudomonas* sp is isolated in 10% of the patients with IIA acquired in the community
B) *Pseudomonas* sp is not a problem in the socio-IIA
C) *Enterococcus faecium* is the microorganism responsible for most of the socio-sanitary IIAs
D) *Pseudomonas* sp is isolated in approximately 5% of IIAs acquired in the community

18. As to the duration of antibiotic treatment in the IIA, it is not false that:

A) It is recommended to maintain the antibiotic treatment 2 weeks
B) If focus control is adequate probably 5 days of antibiotic treatment is sufficient
C) It is recommended to maintain the antibiotic treatment until the fever disappears
D) Prolonged antibiotic treatment is associated with better results

19. Male 91 years old, with HBP, benign prostatic hypertrophy and hypercholesterolemia. He lives in Chronic Care Residence and is a permanent SV carrier. He has had previous ITUs in recent years. He comes our hospital for sepsis of urinary origin. Which of these antimicrobials would you choose as an empirical treatment?

A) Ertapenem
B) Meropenem
C) Ciprofloxacin
D) Piperacillin-tazobactam

20. In the previous patient, what would you do about the bladder catheter replacement following the published guidelines?

A) It is not necessary to change it, since there are many possibilities of bacteriuria in this patient.
B) I must change it before setting antibiotic treatment.
C) I must change it once the antibiotic treatment has begun.
D) Before changing it, I must put an antibiotic through a bladder catheter.

21. In the urine culture collected prior to the start of antibiotic treatment, more than 100,000 cfu / ml of *E. coli* ESBL are isolated as well as in blood cultures and report as sensitive to AMC and P/T (BL-BLI). Indicates the correct answer.

A) It seems to me that Microbiology department that has made that report is not reliable, since enterobacteria with ESBL are never sensitive to BL-BLI.
B) I think that I should not change the antibiotic treatment with meropenem, because there is bacteremia.
C) There are studies that show that, in the case like that of this patient, the prognosis is the same with a broad-spectrum carbapenemal as with a BL-BLI.
D) I do not think it appropriate to change to BL-BLI, but since I have been taught to adjust treatment (de-escalation), change to ertapenem. The incidence of *E. coli* in postoperative peritonitis in Spain is <3%

22. Which of the following is NOT correct regarding the general principles of antibiotic use?

A) Prescription of antibiotics is a decision-making process
B) The prescription of antibiotics is somewhat dynamic, and must be adapted to the course of infection and the information available
C) Clinical, microbiological, epidemiological and pharmacological aspects must be integrated into the decision-making process
D) The logistics and organizational circumstances of the center DO NOT influence the decision making of antibiotics

23. On the setting of antibiotic treatment, point to the CORRECT option:

A) Antibiotic treatment should be adjusted using the antibiotic with the lowest spectrum that indicates the antibiogram
B) The antibiotic (spectrum) adjustment should take into account the representativeness of the microbiological results
C) It is not possible to adjust the empirical treatment (eg reduce spectrum) when microbiological tests do not produce any results
D) It is always better to choose to antibiotic with lower MIC

24. For the duration of antibiotic treatment, indicate the CORRECT option:

A) Once initiated an antibiotic treatment must be completed a cycle to avoid the emergence of resistances
B) The standard duration of antibiotic treatment for community-acquired pneumonia is 10 days
C) The standard duration of acute otitis media, especially if bilateral is 10 days
D) Biomarkers do not help determine the duration of antibiotic treatment

25. Based on the results Based on the results of the OPAT-TADE Registry, the most commonly used parenteral antimicrobials in Home Hospitalization are:

A) Ceftriaxone, levofloxacin and daptomycin
B) Ertapenem, ceftriaxone and ceftazidime
C) Ertapenem, ceftriaxone and piperacillin / tazobactam
D) Ceftriaxone, ertapenem and teicoplanin can be treated with oxacillin

26. What antibiotic is NOT stable at room temperature after reconstitution and therefore can not be infused by electronic infusion pump at home.

A) Vancomycin
B) Ceftazidime
C) Meropenem
D) Cefazoline

27. State which of the infusion modes is NOT appropriate for the indicated antimicrobial.

A) Ertapenem - gravity
B) Daptomycin - bolus
C) Ampicillin - elastomeric device
D) Tigecycline - electronic pump. It is also resistant to erythromycin

28. Which of the following diagnostic techniques is faster to diagnose *C. parapsilosis* candidemia?

A) Traffic light PNA-FISH
B) Direct maldi-tof on blood culture
C) Candida T2
D) Filmarray

29. Which of the following species of Candida takes longer to grow in blood culture bottles?

A) C. *albicans*
B) C. *auris*
C) C. *parapsilosis*
D) C. *glabrata*

30. Which of the following antifungals is more resistant to *Candida auris*?

A) Amphotericin B
B) Fluconazole
C) Caspofungin
D) Anidulafungin

31. Which of the following species of Candida is less prevalent in haematological patients than in ICU patients?

A) Candida *krusei*
B) Candida *tropicalis*
C) Candida *parapsilosis*
D) Candida *glabrata*

32. What factor of the following do you think has a lower impact on survival in neutropenic patients with candidemia?

A) Persistence of neutropenia
B) APACHE II
C) Age
D) Removal of catheter

33. To which of the following statements do you agree with regard to granulocyte transfusion in neutropenic patients with candidemia?

A) Its low effectiveness limits its application at present
B) Reduces the number of infections but is associated with significant side effects
C) Well-designed clinical trials have not confirmed its efficacy.
D) The evidence is limited but non-comparative studies have shown favorable results in certain patients and conditions

34. The treatment of AI ...

A) It must be initiated early, on suspicion of the disease while performing the diagnostic tests
B) It must be started when I have the diagnostic confirmation
C) In patients with "halo" can not be expected, in the rest depends on galactomannan
D) It should be initiated in all haematological patients with more than 5 days of fever that does not respond to antibiotics

35. Which of the following statements is false?

A) Voriconazole is the treatment of choice for invasive aspergillosis
B) Isavuconazole has been shown to be equivalent in effectiveness but with less toxicity than voriconazole for the treatment of AI.
C) Combination therapy with azoles and echinocandins should be reserved for patients with CNS involvement
D) Liposomal amphotericin should be the treatment of choice in patients with toxic hepatitis

36. Monitoring of antifungal drugs in the treatment of invasive aspergillosis

A) It is a tool that has been scientifically proven to improve the prognosis and decrease the toxicity of the drugs
B) In the case of voriconazole it is recommended to perform between days 7 and 12.
C) In the case of amphotericin B, it is important to maintain levels above 1.5 mg/L and below 5 mg/L.
D) All are true

37. Which of the following pairings between alternative approaches or strategies in the treatment of infections and their mechanism of action, product or substance is incorrect?

A) Anti-virulence strategies / monoclonal antibodies.
B) Modulation of the microbioma / Fecal transfer
C) Biological Therapy / Bacteriophages.
D) Vaccines / Quorum - Quenching.

38. Among the examples of agents whose strategy is the mechanism of inhibition of toxins or secretion systems, bezlotoxumab is a monoclonal antibody directed against:

A) Alpha-hemlysin of S. aureus.
B) Bacillus anthracis toxin.
C) Shiga Toxin 1 and 2 of E. coli.
D) Clostridium difficile toxin B.

39. With respect to vaccines against healthcare-related infections and multidrug-resistant pathogens, one of the following statements is false:

A) They could achieve collective or group effect ("herd")
B) It would be difficult theoretically the appearance of resistances ("resilience")
C) The vaccines against S. aureus and P. aeruginosa are already available in daily clinical use.
D) The immune response may be poor in the elderly and immunosuppressed.

Correct answer sheet

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	a	b	c	d
1	X			
2				X
3			X	
4		X		
5				X
6			X	
7				X
8	X			
9		X		
10		X		
11				X
12			X	
13			X	
14		X		
15				X
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29				X
30		X		
31			X	
32				X
33				X
34	X			
35			X	
36	X			
37				X
38				X
39			X	