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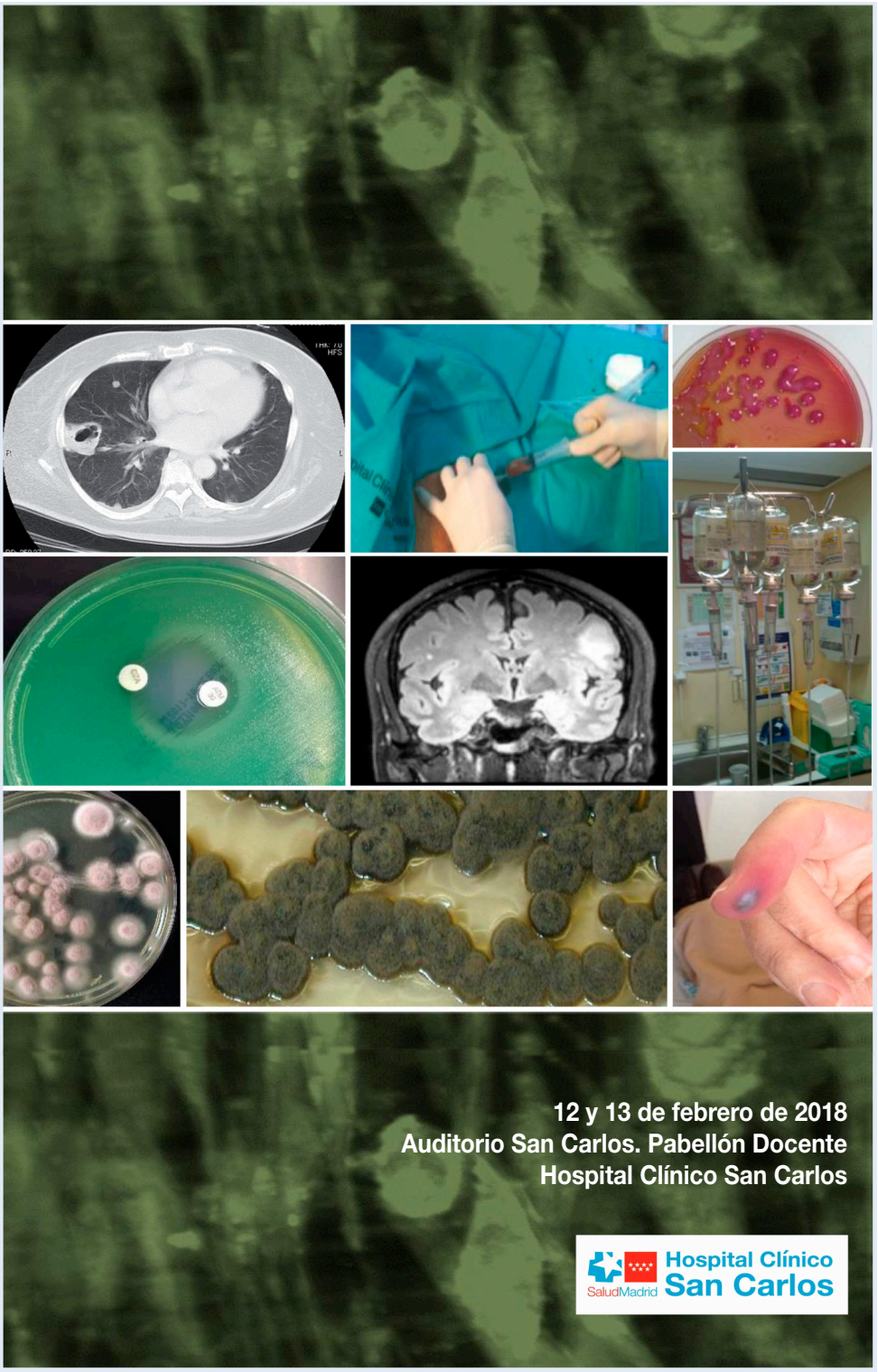

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Quimioterapia

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ABSTRACT

VIII Updating Course of Antimicrobials and Infectious Diseases has reviewed useful microbiological, epidemiological and clinical aspects for a current approach of infectious pathology. Present manuscript summarizes a chronicle about the main infection related meetings during 2017 (ECCMID, IAS, ASM and ID Week). In addition, the course proposed a practical approach for understanding different type of pathogens and our selected topics this year were the epidemiology of bacterial nosocomial infection, a practical approach to *Clostridium difficile* infection patients, a two year selection of the top ten papers about fungal infection and an update in fungal biofilms. Finally, proffesors made a practical approach by main clinical syndromes like sepsis, infections in oncohematological patients, CNS infections in immunosuppressed patients and reviewed the top ten papers in transplant infectious diseases and infection control during the last two years.

Key words: Infectious diseases, current concepts

Actualización en patología infecciosa 2018

RESUMEN

El VIII Curso de Actualización en Patología Infecciosa y Antimicrobianos de Uso Clínico revisó aspectos microbiológicos, epidemiológicos y clínicos útiles para un enfoque actual de la patología infecciosa. El manuscrito actual resume una crónica sobre las principales reuniones relacionadas con la infección durante 2017 (ECCMID, IAS, ASM y la Semana de identificación). Además, el curso propuso un enfoque práctico para comprender diferentes tipos de patógenos y nuestros temas seleccionados este año fueron la epidemiología de la infección nosocomial bacteriana, un enfoque practico en pacientes con infección por *Clostridium difficile*, una selección de los diez mejores artículos sobre infección fungica en los ultimos dos años y una actualización en biofilm fungicos. Finalmente, los profesores realizaron un abordaje de práctico por síndromes clínicos principales como sepsis, las infecciones en pacientes oncolohematológicos, las infecciones del sistema nervioso central en pacientes inmunosuprimidos y revisaron los diez articulos mas importantes en enfermedades infecciosas de trasplantes y control de infecciones en los ultimos 2 años.

Palabras clave: Enfermedades Infecciosas, conceptos actuales

INTRODUCTION

Last february, the VIII 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-02113.6/2018, 1 credit) and endorsed by the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), the Spanish Society of Chemotherapy (SEQ) and the Madrid Society of Clinical Microbiology (SMMC). This year the course attracted more than 500 multidisciplinar proffesionals 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 questionnaire with the evaluations made by the students and a sheet of correct answers to being able to contrast the results. Revisions have been grouped under 3 headings to guarantee a greater educational character. First of them was

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and update in infection related meetings during 2017, and we selected the European Congress of Clinical Microbiology and Infectious Diseases or ECCMID, the American Society of Microbiology Microbe or ASM Microbe 2017, the International AIDS Society meeting or IAS 2017 and the Infectious Diseases Week or ID Week 2017. For the second section, practice approach by type of pathogens, we selected this year four topics: epidemiology of bacterial nosocomial infection, practice approach to *Clostridium difficile* infected patients, top ten papers in fungal infection in the last two years and an update in fungal biofilms, from bench to bedside. For the last heading about a practice approach by main clinical syndromes, we selected sepsis and biomarkers, a current perspective of infections in oncolo-hematologyc patients, a review of top ten papers in transplant infectious diseases and infection control and lastly a review of CNS infections in inmunosuppresed patients.

UPDATE IN INFECTION RELATED MEETINGS DURING 2017

The increase in antimicrobial resistance represents a serious health problem which leads the scientific community to the development of new diagnostic techniques as well as new antimicrobials. Dr. Cercenado analyzed the most important contributions presented at the last ECCMID related to these topics [1]. In relation with the new diagnostic techniques, one of the major advantages is the ability to detect different microorganisms directly from clinical samples in a short time. For instance, LAMP (loop-mediated isothermal amplification) detects virus, bacteria, fungi and parasites in a total turn-around-time between 50 to 90 minutes resulting in a greater specificity, sensitivity than conventional PCR. Another example could be the molecular assays based on the detection of microorganisms by real-time PCR. Among these, Dr. Cercenado stressed the syndromic microarray-based nucleic acid assays. Antigen-based detection by rapid immunocromatographic tests (ICT) is also a good alternative to detect in 10 minutes different microorganisms, carbapenemases and other proteins from cultured bacterias [2]. The new diagnostic applications of data generated through the nucleic acid sequencing technologies, "next-generation" sequencing (NGS), could be an important approach in septic patients.

Regarding to antimicrobial resistance, she stressed the emergence of chromosomal and plasmid mediated resistance to polymyxins due to the *mcr-1* gene. These antibiotics are sometimes the last resort for the treatment of some mutidrug resistant (MDR) organisms, such as the carbapenemase-producing ones, which have been the cause of multiple outbreaks around the world. She analyzed other studies that describe the vertical and horizontal dissemination of the carbapenemase NMD-5, the threat of OXA-48 dissemination through *Klebsiella ascorbata*, the emerging resistance during the treatment with ceftazidime-avibactam mediated by different resistance mechanisms as efflux pumps or blaKPC mutations [3], among others. She also mentioned the plasmidic transporter *optrA* gene, a new linezolid-resistance mechanism carried by some enterococcus strains, and she also analyzed the prevalence of antibiotic resistance in *Helicobacter pylori*. Some of the new antimicrobials are: zidebactam, a penicillin-binding protein inhibitor that enhances betalactams activity against *Klebsiella pneumoniae* (Moya B, et al; P1300). Cefiderocole has activity against MDR Gram-negative microorganisms, meanwhile eravacycline and omadacycline have activity against Gram-positive bacterias at the same time. She highlighted octapeptins and apramycin as less nephrotoxic alternatives than polymyxin and other aminoglycosides, respectively.

Dr. Candel tried to resume te ASM Microbe 2017 which took place in New Orleans (US). The main topics presented during the conference focused on the treatment of infectios by differents microorganisms. Researchs about infections caused by Gram-positive bacteria showed that the activity of ceftaroline had high clinical success rates comparing ceftaroline and ceftriaxone in pneumonia. Other promising agents, oritavancin and dalbavancin, resulted more effective than vancomycin against Gram positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Sun 33). Moreover fusidic acid achieved microbiological and clinical success against MRSA, MSSA, and methicillin-resistant or susceptible coagulase negative *Staphylococcus* (Sat 56). Concerning Gram-negative infection, specifically CPE, plazomicin activity showed less resistence than gentamicine and amikacin, and also got reductions in mortality and toxicity (Martins A). With reference to a Canadian study (Fri 48), ceftazidime-avibactam was more active than ceftolozane-tazobactan against Gram-negative bacteria, with te exception of *P. aeruginosa*. The new cephalosporin-siderophore drug, cefiderocol, was evaluated against more than 1.000 Gram-negative bacilli not susceptible to meropenem, more than a half carrying a carbapenemase, and it showed high activity (Sun 25). It was notably, however, that only 58.3% of NDM-1 producing Enterobacteriaceae and 85.7% of GES producing *A. baumanii* were susceptible (Sun 11). Recent antimicrobial agents against ESKAPE pathogens were presented such as monobactams (LYS228) and aryloxazolidinone-linked bacterial topoisomerase inhibitor (ACT051) (Sat 297, 261) as well as novel antifungical drugs against pathogenic yeast and filamentous fungi like novomycin (NP339), VL-2397 and VT-1161 but they are still in preclinical phases.

Almost everywhere in the world, HIV first treatment lines consist in a combination of three drugs. New antiretroviral (AR) drugs are being developed to provide better alternatives to this tritherapy. Dr. Estrada presented a selection of communications of The International AIDS Society meeting or IAS 2017, that evaluate the safety and efficacy of these treatments, as well as epidemiological aspects of HIV infection. In this context, he commented the situation of HIV in Swaziland [4]. The generalization of treatment in this area of high prevalence from 2011 to 2016 drastically reduced the incidence of HIV and doubled the number of patients with viral

suppression, establishing generalization as a way to partially control the HIV epidemic in Africa. Tsepamo study [5] was also reviewed, it analyzes the use of efavirenz (EFV) and dolutegravir (DTG) during pregnancy, finding both safe to use with a low risk of fetal toxicity and proposing DTG as an alternative to the traditionally used EFV. Finally, Dr. Estrada presented new AR drugs which tend to simplify the therapy using different strategies, such as single pill combinations, intramuscular (IM) administration or dual therapies. These regimens include new drugs like the integrase inhibitor bictegravir [6,7] or darunavir [8], a protease inhibitor. They showed a high genetic barrier to resistance, low toxicity and improvement in bone mineral density. Carbotegravir / rilpivirine combination administered in IM dose [9], particularly relevant in terms of patient compliance, allowing the coverage of the whole treatment when applied every 2 month. And two-drug treatment strategies, such as DTG / rilpivirine [10] found to be effective and having lower toxicity than the classic tritherapy.

In the last few years there has been a rapid increase of multidrug-resistant (MDR) bacterias, becoming a major concern worldwide. This problem led Dr. Emilio Bouza to introduce some of the new drugs presented on the ID week congress 2017 held in San Diego. These new antimicrobials are currently on trial, and hope to become a useful resource in cases of MDR bacterias and treatment of complicated skin and soft tissue infections. Among these drugs, the doctor highlighted some antimicrobials in phase three of development, such as delafloxacin, a quinolone with activity against MRSA and Gram-negatives including *Pseudomonas aeruginosa* and atypicals, and plazomycin, a new aminoglycoside resistant to inactivating enzymes and with lower toxicity than other aminoglycosides. Eravacycline, a new tetracycline in early development, not affected by the TET M pump was also presented, and two combinations of a carbapeneme with beta-lactamase inhibitors: meropenem-vaborbactam and imipenem-relebactam, which are active even against KPC type carbapenemases. After reviewing these and some more drugs, Dr. Bouza commented aspects of Gram-positive and Gram-negative infections. Regarding Gram-positive baterias, he stressed the relevance of MRSA and enterococcal bacteremias, pointing out the high frequency of colonic lesions in patients with *Enterococcus* spp bacteremia and the need of a colonoscopy on those patients. *C. difficile* infection and the controversy of its diagnosis was also highlighted, as well as studies that showed higher probability of recurrence in those patients with low blood antitixin B titre, the implementation of lyophilized faecal microbiota transplantation or the use of ribaxamase, an oral beta-lactamase that protects intestinal microbiota. Among Gram-negatives he discussed the management of patients with cystic fibrosis caused by *P. areugionsa* and dosage in children aged between 12-18 years. Finally, Dr. Bouza commented his interest in a study about the impact of decolonization in patients that are going to undergo herniorrhaphy, and the desirability of studying the nasal carrier stage.

UPDATE IN PRACTICAL APPROACH BY TYPE OF PATHOGENS

Multidrug-resistant (MDR) microorganisms are a major threat for human health nowadays. As Dr. Cantón exposed there are ongoing strategies to fight this increasing problem, such as the "One Health" strategy, a worldwide program that aim to prevent and control the antimicrobial resistance emergence and dispersion [11]. Particularly, nosocomial infections are a major challenge, due to the high number of patients affected, the increasing mortality rate and the variety in the incidence and prevalence of this type of infection. When the Study of Prevalence of Nosocomial Infections in Spain (EPINE, "Estudio de Prevalencia de las Infecciones Nosocomiales en España") data is compared with life-threatening species reported by WHO [12], a strong correlation can be observed where the majority of microorganisms belong to the ESKAPE group. Moreover, microorganisms included in the Critical Category by the WHO (causing severe infections such as bloodstream infection) like *P. aeruginosa,* have a strong presence in nosocomial infections (9.6% in 434 patients, according to EPINE data), showing the importance of bringing new solutions to the problem.

The presenters summarized the evolution of resistance (2013-2016) in the most important microorganisms responsible for nosocomial infections [13]. The major resistance percentage was reported for third-generation cephalosporins, fluoroquinolones and aminoglycosides in carbapenemase-producing *Klebsiella pneumoniae* and the *Escherichia coli* combined resistance to these antibiotics has increased in this period. While in many European countries there has been a slight decrease in the combined resistances of MDR *P. aeruginosa*, in Spain this percentage has increased. Regarding MDR *A. baumannii*, the situation has aggravated in the past years, in Spain, resistance for invasive isolates is higher than 50%. Related to Gram-positive bacterias, a decrease in the percentage of MRSA is observed. However, a third of the European countries including Spain, show a percentage higher than 25%. Vancomycin-resistant *Enterococcus faecium* prevalence has increased in Europe, despite this, the percentages in Spain remain lower than the average.

Dr. Cobo reviewed the most relevant aspects regarding *Clostridium difficile* infection (CDI). First, he highlighted the importance of performing an adequate interpretation of diagnostic tests to define a case as an ICD episode. Then he continued by exposing the consequences of the decision to treat, such as the profound effect on the diversity of the human intestinal microbiota, as it favours colonization by enterococci and antibiotic-resistant enterobacteriaceae [14]. After that, he presented the characteristics of patients with high risk of recurrences [15] because high cost of new drugs (fidaxomicina and bezlotoxumab) makes it necessary to make an appropriate selection of patients susceptible to be treated with these drugs. Finally, he made a series of recommendations for the supervision of CDI cases diagnosed in health institutions, according to the scientific evidence that shows benefits of "CDI stewardships" [16].

In her presentation, Dr García Vidal reviewed the most relevant articles on fungal infection published between 2016 and 2017. Firstly, Dr García Vidal addressed the main characteristics of *Candida auris* infection, including the genetic similarity between the different strains isolated in nosocomial outbreaks, the prolonged colonization period of patients before the infection ocurred, the widespread contamination of multiple surfaces in the healthcare environment, the high mortality rate (>50%) registered for all the infected patients worlwide including those from the first Spanish outbreak and the high antifungal resistance displayed by the microorganism (the majority of strains were resistant to fluconazole, almost half of the strains were resistant to amphotericin B, two strains were pan-fungal resistant and only a few strains were resistant to itraconazole and posaconazole or echinocandins) [17]. Moreover, the increasing evidence showing the relationship between new biological therapies and a higher risk of fungal infection was also addressed. In this concern, studies evaluating the rate of fungal infection following anti-IL17 monoclonal antibody and tirosine-kinase inhibitor therapies have raised an international concern about this serious side effect [18].

On the topic of new antifungal therapies, Dr García Vidal focussed on the new echinocandins that will be available in the coming years, displaying a better Pk/Pd profile, and on the recently approved therapy against aspergillosis and mucormycosis: isavuconazole. Regarding isavuconazole effectiveness to treat aspergillosis, the SECURE non-inferiority trial was presented [19]. Other studies addressing the efficacy and safety of isavuconazole for the treatment of mucormycosis were commented. In addition, the new perspectives offered by the development of new immunological approaches in the treatment of invasive fungal infection were outlined, such as the new experimental models based on the chemical blockade of chemokine receptor CCR1. Finally, Dr García Vidal discussed about several important topics concerning the antifungal therapy such as: the value of the empiric use of micafungin in patients with ICU-acquired sepsis who had *Candida* colonization and multiple organ failure, the association registered between oral fluconazole and spontaneous abortions that should preclude the use of this therapy during pregnancy, and the new role of echinocandins in the early initial treatment of candidemia caused by urinary tract source.

Speaker J. L. del Pozo´s presentation was about fungal biofilms (FB). He started introducing the subject as a FB being a community of microorganisms embedded in a self-produced matrix. It helps pathogens stick to foreign bodies and mechanically isolates them from antibiotics and immune cells. It presents a serious problem in infections of medical devices such as pacemakers and catheters. Most commonly (70%) it is produced by coagulase-negative staphylococci but also fungi, predominantly *C. albicans* or other *Candida* species [20]. Next he highlighted the clinical relevance of FB formation. When bloodstream infection occurred in intensive care units [21] *Candida* species was the fourth causal agent detected (9%) and was associated with the highest crude mortality rate (39.2%), especially when the pathogen is *C. krusei* (59%). FB formation was found to be direct predictor of mortality. The reason behind such data may be the resistance to antifungals via physical barrier effect that FBs provide and the persistence of low metabolic rate cells in it. Nonetheless there is a silver lining in the form of antifungal lock technique with caspofungin and micafungin when a central catheter is involved [22]. He continued summarizing different treatment options. In *Candida* FBs case, antifungal combinations like amphotericin B/posaconazole show high in vitro activity. Frequently *Candida* and *S. epidermidis* in the skin or *Streptococcus* spp. in the oral cavity form a mixed FB. In it synergic interactions between the microorganisms may occur both increasing their antimicrobial resistance. He concluded by focusing on the new research opportunities recent advances present and the need for further investigation in the area of drug-biofilm interactions.

UPDATE IN PRACTICAL APPROACH BY MAIN CLINICAL SYNDROMES

Sepsis identification and management in the initial clinical assessment can determine patient´s prognosis. There are some discordances about clinical management recommendations done by IDSA (Infectious Disease Society of America), SSC (Surviving Sepsis Campaign) and many studies. Dr. González del Castillo did the review of these discrepancies remarking therapeutic and management agreement points that can be advised to reduce the high morbidity and mortality of this entity. Sepsis diagnosis can be overused or missed indistinctly [23], his complex physiopathology and the increase of the aged population attended give rise to atypical analytic and clinical manifestations. Several systematic reviews and meta-analyzes advice the combination of risk stratification scales [24], qSOFA (quick sequential organ failure assessment) showed to be better in prognostic risk while SIRS (Systemic Inflammatory Response Syndrome) is an adequate tool for infection diagnosis. Being sepsis a dynamic process, it can be recommended the monitoring of these scales more than one time during the first hours of episode [25]. The 3-hour bundles (measuring lactate, taking blood cultures and administration of antibiotics) are the most relevant actions to achieve a low mortality risk [26]. Intervention has to be done to avoid antimicrobial delays [27]. For this reason the implementation of a sepsis code in ER can reduce the mortality in facts.

According to SSC guideline antimicrobial treatment have to be started as soon as possible once infection is identified in septic shock and sepsis patients, neverthless IDSA advices just to start antibiotherapy in sepsis patient (without shock) once all preliminary studies are concluded, with the target to reduce the antibiotic overprescription. Another difference is that SSC recommends to use 2 antibiotics in septic shock until resolution or improvement of case, independently of susceptibility, and IDSA suggests to adjust this bitherapy to monotherapy once susceptibility is available. Dr González del Castillo said that the attempt to homogenize definitions

and therapeutics attitudes in heterogenous profile of patient explain the appearance of these controversies. Four points can be remarked for the approach of septic patient [28, 29]: identify the site of infection, source control, immunological status and the existence of septic shock. As a conclusion Dr. González del Castillo said risk score scales and biomarkers (lactate, proadrenomodulina, procalcitonin) have to be considerer together since the beginning to stage severity as soon as possible, cultures have to be taken, start antibiotic and source control stablished. About the different recommendation of guidelines, doctor advocates to start early the antibiotic treatment even in sepsis patient (without septic shock) because the benefit of one initial single dose is higher than the risk of side effects.

Dr. Martinez Sagasti made a review about how some biomarkers can reduce the level of uncertainty in the making decision process at some phases of sepsis, including prompt identification of septic patients, early initiation of empiric broad-spectrum antimicrobials, regimen and duration. For example, he explained that obtaining lactate in the initial stages of suspected sepsis is crucial and should be re-measured because it has proven to be a useful tool to know if the clinical course of sepsis is being favorable [30]. Other biomarkers such as PCT with very high values (>10 ng/mL) suggest a significantly increased risk of sepsis and/or septic shock and low values (<0.2 ng/mL) practically rule out bacteraemia with a negative predictive value (NPV) >98%. And also, low PCT levels (<0.2 ng/mL) in cases of respiratory infection without organ dysfunction can prevent the onset of unnecessary antibiotics. In this context, the PCT has proved useful because it becomes a tool that reduces the level of physician´s uncertainty when deciding to stop antibiotics [31]. Finally, he emphasized how MR-ProADM has shown to have a predictive capacity of 30-day mortality much better than lactate, PCT or PCR warning about the possible poor evolution of patients who apparently had a good prognosis based on lactate levels [32].

Dr. Ruiz Camps, from the Vall d'Hebron University Hospital, selected the top ten articles published in recent years on infections in onco-hematological patients. In relation to bacterial infections and resistance to antibiotics, she highlighted: β-lactam/ β-lactamase inhibitors (BLBLIs) as carbapenem-sparing alternatives for the treatment of bloodstream infection (BSI) with extended-spectrum-β-lactamase (ESBL) [33], prophylaxis with fluoroquinolones and the possibility of reducing unnecessary exposure to antimicrobials [34]. With respect to viral infections, several studies evaluated safety and efficacy of letermovir to prevent CMV infection when used up to 100 days after transplantation [35]. Next, she reviewed novelties in fungal infection, mainly in new risk populations and increase of *Pneumocystis jirovecii* infections. Finally, she presented the impact on infection of novel onco-hematological treatments such as Bruton tyrosine kinase inhibitors and anti PD-1 agents.

On his presentation, Dr López Medrano reviewed the most recent and relevant literature regarding the solid organ transplant infectious diseases. On the topic of viral infection, Ganciclovir-resistant (GCV-R) cytomegalovirus (CMV) infection associated risk factors, the convenience of doubling the dose of annual influenza vaccination (TRANSGRIPE 1-2 clinical trial) and the deliberated hepatitis C virus transmission through kidney transplantation followed by treatment with direct acting antivirals were presented. Regarding the bacterial infection in solid organ transplant recipients, a study by Dr López Medrano and his colleagues from the Hospital Universitario 12 de Octubre (Madrid, Spain), showed that asymptomatic bacteriuria (AB) in kidney transplanted patients were seldomly followed by symptomatic urinary tract infection (3,6%), that AB episodes were cleared spontaneously in one out of three patients and that one third of the pyelonephritis were not followed by an AB episode. From that observations it was concluded that AB systematic screening and treatment rendered no apparent benefit [36]. On the topic of fungal infection, a multinational retrospective cohort study including 29 hospitals from 10 different countries, performed by Dr López Medrano and his colleagues was presented. The study addressed the risk factors, clinical presentation and determinants of mortality of invasive pulmonary aspergillosis (IPA) in kidney transplant recipients. The authors concluded that pretransplant chronic obstructive pulmonary disease (COPD), impaired graft function and the ocurrence of bacteriemia were risk factors for developing IPA. Moreover, the diagnosis of IPA within the first 6 months after transplantation and bilateral involvement at diagnosis were independent predictors of mortality, whereas the initial use of voriconazol showed a protective effect [37,38]. Later, Dr López Medrano addressed the latest data available on new global cell-mediated immunity assays and their risk prediction capability for infection in transplanted patients.

Finally, Dr López Medrano analysed the three most recently published guidelines regarding infection in solid organ transplanted patients. These included an expert consensus document concerning the management of CMV infection, new recommendations about the management of ESBL-producing and carbapenemase-producing bacteria, and recommendations on the prevention and management of endemic diseases such as tuberculosis, Chagas disease, leishmaniasis, malaria, strongyloidiasis, schistosomiasis, traveler's diarrhea, arboviruses, endemic fungal infections and viral hepatitis.

Speaker E. Calbo presented a selection of the top ten recent papers in infection control. She began discussing hand hygiene (HH) [39]. with a study that evaluated the effect of educating patients on care personal's HH compliance. It was found an overall bun not statistically significant increase in HH compliance of HCW from 65 to 74%. Also hand rubbing for 15 seconds was not inferior to 30. She continued by highlighting studies in hospital outbreaks. Examples were a comparison of three room disinfection strategies [40] on acquisition of *C. difficle* (CD) or multi-drug resistant bacteria (MDR). It was found that greatest risk reduction occurred when UV-C plus standard disinfection was applied in MDR and bleach in CD, having UV-C no additional effect in CD. Other studies focused on fomites like a textiles from a laundry as

a source of zygomicetes in Hong-Kong or transmission of *M. chimaera* in cardiac surgery patients by heater-cooler units produced in a German factory. Special attention was paid to contact precaution (CP) and duration of colonization by MDR. and CD. A meta-analysis [41] on discontinuing CP for MRSA and vancomycin resistant entorocci has not resulted in a detectable increase in infection rates. It was not clear whether low CP compliance or low transmission rate with current hygiene protocols was the cause. Finally she discussed an article on antimicrobial stewardship. In that study [42] authors made continuous educational interventions over a 5-year period in a tertiary hospital. It yielded a significant reduction in antibiotic consumption and parallel to it, decrease in the incidence density of candidaemia and its mortality.

Central nervous system (CNS) infections appear in major proportion in immunocompromised patients (with solid cancer, hematological disorders and transplant recipients), neverthless their diagnostic is often complex and delayed due to a frequent atypical clinical presentation. The symptoms of CNS in these patients can be masked or mimicked by metabolic disturbances, effects of antineoplastic treatment and immunosuppressive drugs. Drug effects, vascular lesions, and radiation effects can appear similar to CNS infections [43]. Even antibiotics can cause neurological presentations, as seizures with imipenem or optic neuropathy by ethambutol. The acute adverse effects of intensive therapies and chronic immunosuppression have led to greater variability of CNS infections.

In the review exposed by Dr. Salavert was described that neutropenia, barrier disruption, B- lymphocyte or immunoglobulin deficiency, and impaired T-Lymphocyte-mediated immunity are predisposing factors to CNS infections in cancer patient. Progressive multifocal leukoencephalopathy (PML) and Limbic encephalitis (LE) are more frequent in these patients with intensive immunosupression.In the treatment strategy of this group of patients should be evaluated vaccinations, transfusin safety issues, community and nosocomial epidemiologic factors, travel and zoonotic expositions and microbial susceptibilities adapation.Patients are in risk previous, during and after cancer or transplant procedure [44].

Regarding hematological disorders, we find more CNS infections in patients with allow HSCT (hematopoietic stem cell transplantation) than auto-transplant, being Fungi and *Toxoplasma* spp. the most frequent agents . It have to be noticed also that PML by JC virus is rare but fatal. DR. Salavert explains that baterial CNS infections are more related to intraventricular devices or after neurosurgical interventions. Diagnosis of CNS infections is based on neuroimaging (MRI), cerebroespinal fluid and in some cases biopsy of focal lesions (*Toxoplasma*, and *Aspergillus* infection). In solid organ transplant (SOT) recipients Dr. Salavert remarked 3 syndromes: post reversible encephalopathy (PRES), post-transplantation lumphoproliferative disorder (PTLD) [45] and immune reconstitution inflammatory syndrome (IRIS). CNS infections are more present after umbilical cord blood transplantation (UCBT) tan HLA-matched sibling donor stem cell transplantation (MST). Dr Salavert exposed one Spanish scientific group study [46] which results showed that 5-year cumulative incidence (CI) risk of developing a CNS infection was 8.2% after UCBT and 1.7% after MST; Fungi (35%), virus (32%), *Toxoplasma* (12%) and bacteria (12%) were the causative microorganism. Symptoms in these patients can be attenuated and their pattern of immunosuppression (neutropenia, function of macrophages) privilege specific infection.

Empirical treatment have to be started as soon as possible [47], and it have to be complemented with improvement of immune statuts and profilactic maintenance doses. There is one timeline linked with the most usual infections in diferent periods after SOT (postoperative phase 1-4 weeks, early post transplant 1-6 months, and late post transplant more 6 months síndromes). Finally Dr Salavert described 2 important groups of factors in CNS infections: prior exposures and the net state of immunosuppression (age, chronic diseases, previous treatment, etc).

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Highlights at the 27th Congress of the European Society of Clinical Microbiology and Infectious Diseases, 2017

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INTRODUCTION

It is difficult to summarize in a few pages the information presented at the last European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) held in Vienna (Austria), last April 2017 [1]. The congress covered the entire field of infectious diseases and clinical microbiology with a huge and interesting amount of information presented. With more than 200 sessions, the key topics were antimicrobial resistance, novel diagnostic techniques, the role of microbiota, and new antimicrobials. In addition, the congress also covered different aspects of the big four in infectious diseases: HIV, viral hepatitis, tuberculosis and malaria. Among a total of 5223 abstracts, this minireview will try to summarize, from an objective point of view, the most important contributions, only focusing in three different aspects: microbiological diagnosis, resistance to antimicrobials, and new antimicrobials.

DIAGNOSTIC MICROBIOLOGICAL TECHNIQUES

In the last decade there has been an increasing number of novel diagnostic microbiological techniques, mainly those based in the detection of microorganisms and some genes implicated in resistance to antimicrobials directly from clinical samples. Among these, the LAMP (loop-mediated isothermal amplification) is an important contribution to the new diagnostic technology. This method amplifies DNA with high specificity, efficiency and rapidity under isothermal conditions. The method employs a DNA polymerase and a set of four different primers that identify six distinct sequences on the target DNA, resulting in a greater specificity than the conventional PCR [2].

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The LAMP technology has been used to detect virus, bacteria, fungi and parasites directly from clinical samples and offers an alternative to bacterial cultivation and PCR. In addition to sensitivity, it is cheap in comparison with PCR techniques and allows the detection of microorganisms directly from blood cultures, BAL, blood and other samples. There have been several studies presented at this meeting related to the application of LAMP. In one study, the LAMP technology was used to detect *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) directly from blood cultures, demonstrating than the test is fast, accurate and cost-effective (Yarayatne P, et al; EV0215). A total of 200 blinded blood culture samples that were positive for Gram-positive cocci (80 methicillin-susceptible SA, 40 MRSA, 55 coagulase-negative staphylococci (CoNS), and 25 other organisms (*Enterococcus* spp. and *Streptococcus* spp.) identified by routine culture-based methods were tested by LAMP assay. All *S. aureus* and MRSA positive DNA specimens were detected within 20 minutes of amplification and the total turn-around-time was less than 60 minutes. The CoNS required longer time of amplification for detection. The streptococci were identified as non-staphylococci. The sensitivity and specificity for detection of *S. aureus* by LAMP were both 100% as compared to culture. Sensitivity and specificity for detection of CoNS were 89.0% and 96.0%, respectively. The positive predictive value (PPV) and the negative predictive value (NPV) for CoNS were 98.0% and 80.0%, respectively. The test performance values for MRSA were 94.7% sensitivity, 97.5% specificity, 94.7% PPV, and 97.5% NPV. The cost per test was around 5 euros and might be considered as a diagnostic option.

Another study analyzed the performance of LAMP for the detection of *Helicobacter pylori* directly from stools (Yarayatne P, et al; EV0218). One-hundred and fifty nine paediatric (< 5-years-old) and 60 adult diarrhoeal stools submitted for routine microbiological testing were tested by LAMP and by real time PCR. Out of 219 specimens tested, 74 were positive and 136 were negative for *H. pylori* by both methods. There were 9 discrepant specimens that were all negative by LAMP

but positive by PCR. The test performance characteristics of the LAMP method as compared to the PCR were as follows: sensitivity, 89.1%; specificity, 100%; NPV, 93.7%; and PPV, 100%. The limit of detection for LAMP was 10^3 colony forming units per millilitre (CFU/ml), the turn-around-time was 90 minutes, and the estimated cost per test was less than 5 euros, being a cost-effective, sensitive, specific and fast method for detection of *H. pylori* from stools. In similar studies, the LAMP was used for the detection of *Mycobacterium tuberculosis* in sputum (Law I, et al; P0076) detecting a bacterial concentration as low as of 10^3 CFU/ml sputum sample in 60 minutes. The test was also used for the detection of *Campylobacter* spp. directly from fecal samples (Florea D, et al; P1009). In a multicenter study, in which a commercialized LAMP test (Orion GenRead Campylobacter) was analyzed, the sensitivity and specificity were 98.02% and 94.4%, respectively and the results were obtained in 50 minutes, demonstrating that this is a rapid and reliable method for the identification of *Campylobacter* species directly from faecal samples and could be an alternative for the conventional phenotypic methods. In other studies the LAMP methodology was used for the detection of virus, fungi, and parasites. In one study (Vergara A; P1901) it was evaluated as a screening tool to detect CMV in 52 critically ill patients in comparison with real-time PCR. The test was performed directly in bronchoalveolar lavage (BAL) samples, boiled BAL samples and after the extraction of DNA. In all cases, the specificity was 100%, and the sensitivities were 58.3%, 66.7%, and 95.8%, respectively.

In another study the LAMP methodology was evaluated for the detection of *Pneumocystis jirovecii* (Alejo I, et al. P0983). A total of 10 BAL samples were analyzed also by real-time PCR and a staining with methenamine silver stain (microscopy) by using different extraction methods. Ten BAL samples positive for *P. jirovecii* by microscopy were processed for DNA extraction by four different methods. The specificity was 100%, however, the test showed a lower sensitivity than the PCR (64% in boiled samples *vs* 95% by using an automated extraction method). The test was performed in 60 minutes. Finally, a commercialized LAMP test was used for the detection of malaria directly from blood (Deleplancque AS; P0786). Although the test does not differentiate the different *Plasmodium* species, it showed a higher sensitivity than culture and if negative it could be used to exclude malaria.

At present, molecular assays based on the detection of microorganisms directly from clinical samples by real-time PCR have reduced the time to organism identification, contributing to optimize antimicrobial therapy and to decrease mortality rates [3, 4]. Among these, the syndromic microarray-based nucleic acid assays have shown high positive-predictive values for detection of organisms in blood, CSF, stool, and other samples. Several studies presented at the ECCMID have assessed the performance of PCR panels (FilmArray, Biofire, bioMérieux) for the diagnosis of meningitis and gastroenteritis. In one multicenter study (Ottiger C, et al; OS0112) a total of 195 CSF samples (136 negative and 59 positive) were analyzed by using a panel that covers six bacteria, seven viruses, and one yeast. Results were obtained in 3 hours and the sensitivity, specificity, positive and negative predictive values were 100%, 95.8%, 86.3%, and 100%, respectively. In the case of gastroenteritis the system, which covers 22 pathogens, was performed in 190 rectal swab specimens and compared with standard procedures (Chapin K, et al. P0999). Percent agreement for bacterial, viral, *C. difficile* and parasitic targets was 93.8%, 70.3%, 57.8% and 40%, respectively.

Antigen-based detection using rapid immuno-cromatographic tests (ICT) are attractive alternatives for the detection of microorganisms, carbapenemases and other proteins and toxins, because they are easy to perform, rapid, and cheap [5]. Several commercial ICT strip tests have been developed for these purposes. In one study an ICT was evaluated for the simultaneous detection of both *Giardia intestinalis* and *Cryptosporidium* spp. (Goudal A, et al. P0761) and showed 89.2% and 86.7% sensitivity, and 99.3% and 100% specificity for the detection of *G. intestinalis* and *Cryptosporidium* spp., respectively. Another commercialized ICT (Synovasure®) was evaluated in a multicenter study for the detection of alpha-defensin in the diagnosis of prosthetic joint infection. The ICT was an easy to conduct and fast diagnostic tool with a high specificity (from 94% to 100%) and a sensitivity from 48% to 75% (Renz N, et al. P1808). Finally an ICT was analyzed for the simultaneous detection of carbapenemases (OXA-48, KPC, and NDM) from cultured bacteria (Glupczynski Y, et al. P0299). In comparison with PCR, the ICT showed 100% sensitivity, positive and negative predictive values, the results were obtained in 10 minutes, it was very easy to perform and could be a cost-effective alternative to PCR methods.

New technologies based on multiplexed automated digital microscopy (Accelerate Pheno™ system) have been developed for the rapid identification of pathogens (1,5 hour) and antibiotic susceptibility (7 hours) directly from positive blood culture broths [6]. In this meeting, a study (De Angelis G, et al; P0997) evaluated this system in comparison with culture-based methods and found that the overall species identification agreement was 88.4% (23/26). A total of 132 microorganism-antimicrobial combinations were included. Category agreement was 93.2% (123/132) and false susceptibility emerged in 3 cases with the combination *Enterobacteriaceae*/piperacillin-tazobactam. The system could be useful in selected patients but at present it is an expensive technology.

In our days, MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight) mass spectrometry is the first-line diagnostic tool in the identification of microorganisms [7]. Future applications of this technique include rapid detection of antimicrobial resistance and bacterial typing. The purpose of a study presented at this meeting was to search, by using MALDI-TOF, for specific biomarker proteins of the ST131 clonal group of multiple drug resistant *E. coli*. They found that the YahO protein with the E34A substitution was a common biomarker protein with prominent ability to discriminate this high-risk bacterial clone responsible for worldwide pandemics (Nakamura A et al; OS 0139).

The high speed and throughput of data generation obtained with the nucleic acid sequencing technologies, "next-generation" sequencing (NGS), constitute a revolution with new diagnostic applications [8]. One study evaluated the diagnostic utility of NGS of circulating cell-free DNA in septic patients (Stevens P, et al; OS0746). Among 254 plasma samples, only 28 (11%) showed a positive blood culture. In contrast, by NGS, 140 samples (55%) showed at least one species (bacteria, viruses and fungi) and time from sample to diagnosis was 24 hours. In the near future, NGS based diagnostics will be a sensitive and specific approach for the diagnosis in septic patients.

ANTIMICROBIAL RESISTANCE

Nowadays, antimicrobial resistance is a major concern for human health. The array of resistant organisms is increasing every day and contributes to high rates of mortality and high economic costs [9]. In recent years, the emergence of chromosomal and plasmid-mediated resistance to polymyxins, which are antibiotics of last resort for the treatment of carbapenemase-producing organisms results in a pan-resistant organism that is potentially untreatable. Plasmid-mediated colistin-resistance is due to the *mcr-1* gene encoding for a phosphoethanolamine transferase [10]. A study presented at ECCMID (Hadjadj L, et al; OS0871) analyzed 32 *mcr-1* strains (25 *E. coli* and 7 *K.pneumoniae*) isolated from different geographical origins from animals and humans. Among *E. coli*, several clones were found, being the most frequent ST4015, ST3997, ST10, ST93, ST48, and ST648. Plasmid carrying *mcr-1* gene was detected in 22 *E. coli* strains (88%) and 2 *K. pneumoniae* strains (28.6%), and one human isolate carried de *mcr-1* gene in the chromosome. Since a wide diversity of insertion sequences allowed this gene to be translocated into the chromosome, the emergence of endemic colistin resistant strains with chromosomic location of *mcr-1* gene must be monitored. Another cause of concern is the dissemination of carbapenemases and the description of multiple outbreaks around the world with the persistence of isolates difficult to erradicate.

One study analyzed the dissemination of the carbapenemase NDM-5 by vertical (*E. coli* ST167) and horizontal (an IncX3 plasmid) transfer during an outbreak. The same plasmid was identified among all isolates (*E. coli, Kleblsiella* spp. and *Enterobacter* spp.) and simultaneously there was an outbreak of a common *E. coli* clone. Both vertical and horizontal dissemination were responsible for the persistence of *bla*NDM-5 in one institution (Feng Y, et al; OS0292). Carbapenemases are also recovered from microorganisms in the environment and can act as reservoirs. One study explored the presence of carbapenemases in a river in Barcelona (Spain). After analyzing 11 sediments and 12 water samples they found different carbapenemases in different Enterobacteriaceae carried in different plasmids. KPC-2 was the most prevalent enzyme, they reported a *K. oxytoca* isolate coproducing VIM-1 and KPC-2, and the first VIM-1-producing *R. ornithinilytica* of environmental origin. The STs identified had not been previously identified in isolates from clinical origin (Piedra N, et al; P1091). In another study, during an active surveillance-screening program for detecting extended-spectrum β-lactamase (ESBL)-carriers, an OXA-48+CTX-M-9-*like* producing *Kluyvera ascorbata* was detected in 6 unrelated patients. The carbapenemase was carried in a plasmid also found in other species. The authors highlight the threat of further nosocomial OXA-48 dissemination through *K. ascorbata* either by clonal transmission or by lateral transfer of a plasmid (Hernández García M, et al; OS0289).

Ceftazidime-avibactam (CAZ-AVI) is one of the few new antibiotics with activity against carbapenemase-producing organisms, however, the emergence of resistance during the treatment with this antimicrobial has been described [11]. One study demonstrated that mutations in blaKPC-3 that emerged during CAZ-AVI treatment of carbapenem-resistant *K. pneumoniae* infections encode novel KPC-3 variants that confer CAZ-AVI resistance, restore carbapenem susceptibility, and function and may be misidentified as ESBL (Nguyen MH, et al; OS0490). Other mechanisms of resistance can also decrease the efficacy of this antimicrobial. In one study, the authors found that AVI is a substrate for the efflux pump mexAB-OprM in *P. aeruginosa*. The overexpression of this efflux pump increased CAZ-AVI MICs of 5 two-fold dilutions without increasing that of CAZ but reducing the activity of AVI against *P. aeruginosa* and demonstrating a role of this transporter in AVI efflux (Chalhoub H, et al; EV0469). The emergence of 16S rRNA methyltransferases (16S RMTases) is a resistance mechanism that confers high-level resistance (MICs ≥256 mg/L) to all clinically-relevant aminoglycosides in Gram-negative bacteria. One study performed in the United Kingdom (Taylor E, et al; OS0298) identified the prevalence of 16S RMTase genes (*armA*, *rmtA-H* and *npmA*) in isolates received at a reference center: 527 (95.8%) *A. baumannii* and 755 (92.4%) Enterobacteriaceae isolates were positive for 16S RMTase genes; *armA*, *rmtB*, *rmtC*, *rmtE*, *rmtF* and various two gene combinations were identified. The vast majority (94.5%, 1211/1282) of 16S RMTase-positive isolates also produced a carbapenemase.

Another multicenter study performed in Greece, showed that among 300 carbapenemase-producing Enterobacteriaceae, 23 isolates (7.7%) carried the *rmtB* (n=22) and *armA* (n=1) genes, and these isolates were resistant to the next generation aminoglycoside plazomicin (Galani I, et al. P0406). This combination of carbapenemase and 16S RMTase genes poses a serious threat to the treatment of multidrug-resistant Gram-negative isolates.

Among Gram-positive bacteria, new resistance mechanisms have also emerged in the last decade. Among 539 linezolid-resistant *Enterococcus* spp. received in a reference center in Germany, 18 isolates (32% of linezolid-resistant *E. faecalis* and 1.4% of linezolid-resistant *E. faecium*) carried the plasmidic and transferable transporter *optrA* gene, enhancing the risk of dissemination of linezolid resistance (Bender JK, et al; P1382).

Helicobacter pylori infection is difficult to treat due to increased resistance to antibiotics. In order to define the prevalence of antibiotic resistance in *H. pylori* in the world, the authors conducted a systematic search of the literature published in the last ten years (Savoldi A, et al; P0719). A total of 59.478 *H. pylori* isolates were included. The prevalence of resistance (2013-2014) was: metronidazole 54.4%, levofloxacin 25.3%, and clarithromycin 25%, observing an increasing time trend of drug-resistant *H. pylori*. Co-resistance to clarithromycin and metronidazole ranged from 1% in Europe to 30% in Southern Asia, confirming the worrisome tendency towards high level of drug resistance to the first and second line antibiotics used for the treatment of *H. pylori*.

Another concern is the emergence of resistance in microorganisms causing sexually transmitted infections. One study analyzed the prevalence of resistance of *Mycoplasma genitalium* to macrolides and fluoroquinolones in Barcelona. Among a total of 85 *M. genitalium* isolates, macrolide resistance mediating mutations were detected in 35% of the *M. genitalium*-positive episodes whereas 8% carried fluoroquinolone resistance mutations, and 3 cases harbored multi-drug resistance to both classes of antibiotics. Men who had sex with men and previous azithromycin treatment were strongly associated with azithromycin resistance. This alarming rate of resistance makes necessary the implementation of combined diagnostic-resistance detection assays for *M. genitalium* (Fernández Huerta M, et al; P1884).

NEW ANTIMICROBIAL AGENTS

The development and introduction of new antimicrobials has slowed considerably in the last decade. Since 16 antibiotics were approved by the FDA between 1983 and 1987, only 2 were approved between 2008 and 2012, and a total of 7 new antimicrobials have been approved since the end of 2012 [12,13]. Some of the new antimicrobials developed and/or approved in recent years are summarized in table 1. Among the new antimicrobials, zidebactam is a penicillin-binding protein (PBP) inhibitor showing potent beta-lactam enhancer activity against the PBP2 of *Klebsiella pneumoniae*, but it is not active against metallo-β-lactamases (Moya B, et al; P1300). Cefiderocole is a novel siderophore cephalosporin active against multidrug-resistant Gram-negative microorganisms including ESBL and carbapenemase-producers, *P. aeruginosa, Acinetobacter baumannii* and *Stenotrophomonas maltophilia* with MIC_{90} values ranging from 2-4 mg/L (Dobias J, et al; OS0561). Cefiderocole is also active against colistin-resistant, ceftolozane-tazobactam-resistant and ceftazidime-avibactam-resistant isolates (Yamano Y, et al; P1316). Eravacycline is a fluorocycline antibiotic of the tetracycline class with activity against multi-drug resistant Gram-negative and multi-drug resistant Gram-positive organisms (Morrissey Y, et al; P1260). Omadacycline is a broad spectrum aminomethylcycline of the tetracycline class with similar spectrum to that of eravacycline, with intravenous and oral formulations, developed for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (Huband M, et al. P1253). Octapeptins are new lipopeptides active against

Table 1 | **Activity of new antimicrobials against Gram-negative microorganisms**

	Enterobacteriaceae					Other Gram-negative bacilli	
	ESBL	AmpC	KPC[a]	OXA-48[a]	MBL[a]	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*
Ceftolozane/ tazobactam	+	-	-	-	-	++	-
Ceftazidime/ avibactam	++	++	++	+	-	++	-
Aztreonam/ avibactam	++	++	++	+	++	+	-
Imipenem/ relebactam	++	++	++	-	-	+	-
Meropenem/ vaborbactam	++	++	++	-	-	+	-
Cefepime/ zidebactam	++	++	++	++	++	++	-
Cefiderocol	++	++	++	++	++	++	+
Eravacycline	++	++	++	++	++	-	++
Plazomicin	++	++	++	++	++/-	++	+
Omadacycline	+	-	-	-	-	-	-
Octapeptins	+	+	+	+	+	+	+
Novarifyn	-	-	-	-	-	-	+
Murepavadin	-	-	-	-	-	+++	-

[a]**Carbapenemases: KPC, OXA-48, metallo-β-lactamases (MBL)**

multi-drug resistant and polymyxin-resistant Gram-negative bacteria and less nephrotoxic than polymyxin B (Blaskovich M, et al. EP0398). Novarifyn is a novel peptide with rapidly bactericidal activity against both Gram-positive and Gram-negative multi-drug resistant pathogens including MRSA and *Acinetobacter baumannii* (Katvars L, et al; P1361). Apramycin is a monosubstituted deoxystreptamine, different in chemical structure from other aminoglycosides, with low nephrotoxicity, active against multi-drug resistant Gram-negative organisms and maintaining activity in the presence of aminoglycoside modifying enzymes and rRNA methylation (Hobbie S, et al; EP0403).

New antimicrobials active against Gram-positive microorganisms include the fluoroquinolones delafloxacin and lascufloxacin, the fluoroketolide solithromycin, and the semi-synthetic pleuromutilin antibiotic lefamulin for oral and IV use, currently in phase 3 trials for the treatment of community-acquired pneumonia in adults (Paukner S, et al; P1331). We know that it is necessary to maintain strategies for a better use of antimicrobials with the objective of slowing the development of resistance, but meanwhile, it is also necessary continuing to develop new antimicrobial agents at a sufficient rate to keep ahead of the bacteria, and we are in the way.

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Highlights in ASM MICROBE 2017 (New Orleans)

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The following manuscript intends to give an overview of the main topics presented during the ASM Microbe 2017 held from June 1 to 6 in New Orleans (LA, US), with special focus on those more novel and/or controversial topics; taking into account the impossibility of summarizing the totality of the communications.

For a better comprehension, the manuscript is divided into four sections: Gram-positive infections, Gram-negative infections, new antimicrobial agents and new antifungal agents.

GRAM-POSITIVE INFECTION

Infections caused by multidrug-resistant Gram-positive bacteria represent a major number of infections in our hospitals. Consequently, new drugs are being investigated and tested, and a large number of studies have been carried out.

The SENTRY surveillance program, as a part of a larger study, measured the activity of fusidic acid against 1,000 strains of methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible coagulase-negative *Staphylococcus* (MS-CoNS), and methicillin-resistant coagulase-negative *Staphylococcus* (MR-CoNS). Samples were collected from different hospitals in the USA. The results showed that only 1.7% of strains were resistant to this antibiotic (Sat-56).

Another project compared linezolid 600 mg/12h versus fusidic acid (FA) 1500 mg/12h during the first two days, followed by 600 mg/12h. Both were oral treatments during 10 days over skin and soft tissue infections. The results showed no-inferiority of FA due to an early clinical response after the first dose during the first 48-72h. FA also achieved microbiological success in 100% of patients who finished the treatment, and there was no difference relative to secondary effects (AAID LB21).

Another large study was conducted in USA under the AWARE surveillance program in the ICU ward with elderly hospitalized patients with pneumonia. The activity of ceftaroline and ceftriaxone was measured in 2.250 pneumonia etiologic pathogens. Ceftaroline was active over all the bacterial pneumonia etiologic agents in the ICU, even against *Streptocccus. pneumoniae* penicillin-resistant. In addition, MICs were lower than with other antibiotics tested (Sun-5, Harris K.; Sun-24).

In the CAPTURE study experience, 188 patients with community acquired bacterial pneumonia (80.9%) and hospital acquired/ ventilator associated pneumonia (19.1%) were treated with ceftaroline fosamil. The results obtained showed a high clinical success rate when using doses of 600mg/12h, and a very low mortality index (Fri-35. Undeani G.).

On the other hand, persistent infection has been subject of clinical concern lately. Oritavancin, dalbavancin and vancomycin were tested against non-dividing MRSA. The bacterial viability was assessed by serial dilution planting, and results were measured by fluorescence microscopy. Oritavancin achieved higher logarithm reduction than vancomycin and dalbavancin (Belley A. et al).

Dalbavacin bactericidal effect, when daily dosing was applied for endocarditis therapy caused by *S. aureus* with elevated MIC, was evaluated in a Pk/Pd murine model. The aim of this study was to investigate if the results could be extrapolated to humans. Different doses were trialed, showing that using high loading doses (300-700 mg) followed by a maintenance dose (30-70 mg), allowed the target attainment to be achieved (Farkas A. Mount Sinai).

In another remarkable study at ASM Microbe 2017, oritavancin was tested against 1.500 strains of Gram-positive bacteria commonly isolated in blood-stream infections (BSI), and bone and joint infections (BJI). Just 2% of the strains were

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resistant to this antibiotic. Overall, oritavancin demonstrated larger *in vitro* potency than comparison agents did. Regarding BJI, oritavancin also demonstrated high *in vitro* activity, including MRSA (Mendes RE. Sun-33; Fri-342).The results suggest that this antibiotic is promising but requires more clinical experience.

Moving on to vancomycin-resistant *Enterococcus* (VRE), it is worth remembering an article published in 2015 with the results of treating bloodstream infections with daptomycin. Authors wrote about the seesaw effect of daptomycin when using in combination with β-lactams antibiotics, in cases in which daptomycin MIC was over 2 mg/L (Moise PA. Clin Ther 2016). Another study was presented, reflecting 177 BSI by VRE and treated with daptomycin at doses of 8-10 mg/kg. Patients were divided in two groups depending on the MIC of daptomycin: MIC ≤ 2 mg/L (n=33) and MIC = 3-4 mg/L (n=144). There was no difference in clinical success, focus control or adverse effects (Fri-217).

By finishing this Gram-positive review, it is worth noting the international study carried out in which tedizolid was tested against 612 strains of Gram-positive cocci obtained from bone infection. All 100% of the strains were susceptible, and showed a MIC < 0.5 mg/L. According to that, tedizolid would be an attractive alternative for treating BJI (Fri-217).

GRAM-NEGATIVE INFECTION

Plazomicin activity, when MIC is tested under non-standard conditions, is comparable to that of amikacin, with a negligible effect of increasing or decreasing the bacterial inoculum, the addition of human serum or lysed horse blood, variations of Mg^{2+} o Ca^{2} concentration and growth in 5% CO_2 atmosphere or at pH of 8. In addition, two known characteristics of the aminoglycosides were confirmed, such as the reduction of their activity under conditions of acid pH or anaerobiosis (Fri-410).

On a Brazilian study (Martins A.) focused on testing the susceptibility to aminoglycosides, with 500 carbapenemase-producing Enterobacteriaceae (CPE) strains, mainly KPC-2 (n=399) and NDM-1 (n=79), plazomicin obtained a lower MIC than the cut-off point in 90% of isolates, with a MIC mode and median below 0.5 mg/L. In the comparative study, gentamicin showed more than 90% of resistance, and amikacin showed an MIC_{50} of 8 mg/L (4 dilutions higher than that obtained with plazomicin).

Another study compared the efficacy and safety of plazomicin treatment for severe infections (BSI, NAP and VAP) produced by CPE. Colistin was used as comparator. Doses used in this study were 15 mg/kg/24h of plazomicin as 30 minutes infusion and 5 mg/kg/8-12h of colistin with a loading dose of 300 mg. Both antibiotics were used in combination with others such as meropenem or tigecycline, with a total treatment length between 7 and 14 days. Plazomicin got reductions in all-causes mortality at day 28, bacteremia related mortality at day 28, toxicity and a greatest microbiological response.

Getting into communications related to β-lactam antibiotics, we start with a study (Fri 53) which tested aztreonam/avibactam (AZT/AVI) activity against 267 strains of class B CPE (120 NDM-like, 82 VIM-like, 27 IMP-like, 22 NDM+OXA-48 like, 8 VIM+OXA-48 like, 6 VIM+KPC and 2 IMP+KPC) obtained from different geographical localizations all over the world. All strains were susceptible to AZT/AVI with an improved activity than aztreonam.

A study from the Mayo Clinic (Karau M.) compared the *in vitro* activity of piperacillin/tazobactam (PIP/TZ), ceftazidime, cefepime, meropenem (MER) and ceftazidime/avibactam (CAZ/AVI) against *Pseudomonas aeruginosa* isolates from patients admitted to ICU ward. CAZ/AVI turned out to be the β-lactam with the highest susceptibility percentage (89.9%), showing a MIC ≤ 4 mg/L in 78.3% of the strains and a MIC ≤ 8 mg/L in 89.9% of total cases. MER obtained 76.8% susceptibility, with 84.1% and 88.4% of the strains showing a MIC ≤ 4 mg/L and MIC ≤ 8 mg/L respectively.

Regarding the activity of CAZ/AVI against *P. aeruginosa* strains obtained from the INFORM global surveillance program of 2015 data was presented (Fri-51). In total, 90.8% of the strains (n = 3.462) were susceptible to CAZ/AVI, increasing to 94.7% when only non-metallo-carbapenemases producer strains were considered (n = 3.319). In addition, among multidrug-resistant strains (MDR) that do not produce metallo-carbapenemases, 30.7% (n = 540) were non-susceptible, showing that there are mechanisms of resistance other than metallo-carbapenemases.

The therapeutic success of CAZ/AVI was also evaluated in a retrospective cohort study among patients at the University of Pittsburg Medical Center (Fri 8) who received 3 or more days of definitive treatment for carbapenems-resistant (CR) *Klebsiella pneumoniae* bacteremia. In this study, the outcomes of those patients treated with CAZ/AVI were compared with those achieved with the rest of the therapeutic options. Clinical success and survival rates were improved among patients treated with CAZ/AVI compared to alternative regimens for CR *K. pneumoniae* bacteriemia. At the same time, CAZ/AVI was associated with lower rates of acute kidney injury than regimens containing colistin or aminoglycosides.

On the other hand, a Canadian study (Fri 48) evaluated the activity of several β-lactams against Gram-negative bacilli obtained from the CANWARD study. According to this study, CAZ/AVI was found to be more active than ceftolozane-tazobactam (CT/TZ) in all cases except *P. aeruginosa*. Another study (Fri 50) showed potent activity of C/T against various resistant phenotypes including extended spectrum β-lactamase (ESBL), colistin non-susceptible, MDR and extreme-drug-resistant isolates.

It was very remarkable a Spanish communication (Sun LB-15), that showed, for the first time, the existence of a resistant strain to these new combinations of cephalosporin-betalactamases inhibitor (CAZ/AVI and CT/TZ) due to the duplication of an aminoacid at the active site of an OXA-2 betalactamase (class D) of the high-risk clone ST235.

Regarding the new combination of meropenem with vaborbactam (MER/VAR), it was reported a study (Fri 58) that showed an improvement of the carbapenemic activity against classes A and C betalactamases, achieving a decrease in MIC of 4 to 6 folds lower than MER. This combination has been approved by the FDA for urinary infections treatment, including pyelonephritis, after demonstrating greater efficacy, safety and tolerance than PIP/TZ. Regarding the preliminary results of the TANGO-1 study (Kaye KS.) on urinary bacteremia, MER/VAR was successful in 83%-100% of the cases at the end of the intravenous treatment (IV), while PIP/TZ obtained 60%-75%. In the case of BLEE carrier isolates, success at the end of IV treatment was 94%-98% and 56%-66% for MER/VAR and PIP/TZ respectively. Patients with a higher Charlson were worse, without differences between both groups (Shorr A.). Regarding the average stay, something similar happened; this was greater in the more comorbid ones, without differences between the assigned treatments (Shorr A.).

Finally, there were many and remarkable communications about cefiderocol, a new cephalosporin drug, characterized by a strong chelating ability to Fe^{3+} as well as siderophores. Cefiderocol penetrates bacteria using iron transporters, present in multiple Gram-negative bacteria, such as enterobacteria and non-fermenting bacilli. A study was presented in which the activity of cefiderocol was evaluated against more than 1,000 Gram-negative bacilli not susceptible to MER, with more than half carrying carbapenemase, mainly OXA-23 (n=543). Cefiderocol showed high activity, with MIC_{50} and MIC_{90} several dilutions below the cut-off point (≤4 mg/L) (Sun 25). It was notably, however, that only 58.3% of NDM-1 producing enterobacteria and 85.7% of GES producing *Acinetobacter baumannii* were susceptible, although the resistant strains showed CMI one fold above the cut-off. In addition, cefiderocol proved to be more active than colistin, CT/TZ, CAZ/AVI and ciprofloxacin (Sun 11).

NEW ANTIMICROBIAL AGENTS

During the last years, there has been special interest in the development of new therapeutic options against ESKAPE pathogens (VRE, MRSA, ESBL and CR *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* sp.).

The optimization of novel monobactams for stability against serine β-lactamases has led to the identification of LYS228. The mechanism of action of LYS228, which is similar to that in aztreonam, consist on binding to PBP3 lowering its affinity to the PBP1AB. LYS228 is highly efficient in the presence of all classes of β-lactamases, and it is not affected by metallo-β-lactamases. It also has good stability against ESBLs, including the cephalosporinases, and also shows high activity against carbapenemases (CTX-M, KPC, OXA) Enterobacteriaceae isolates. It has been found mutations in regulators cell wall stress and efflux pumps. It has a preclinical pharmacokinetic profile, pharmacokinetic/ pharmacodynamic profile similar to aztreonam. Phase I studies are ongoing (Sat-297).

The New Agents Discovery Summary Session presents ACT051, a novel aryloxazolidinone- linked bacterial topoisomerase inhibitor (NBTIs), with heavy activity against ESKAPE pathogens. Typical NBTIs, have activity against VRE, MRSA and *A. baumannii*. ACT051 has potent activity against all ESKAPE pathogens, and retained activity against resistant strains to major antibiotic classes. (Sat-261, 262, 263, 264, 265. Sun-210).

Finally, the ARB- Antibiotics Hybrids, presented by the Kings College of London. They introduce a work hypothesis, talking about de association between two molecules, one of them (low molecular weight proteins) which disrupt the efflux pumps function, leading to elevated intracellular concentration of the second molecule (e.g. fluoroquinolone). These studies are still in the design phase.

NEW ANTIFUNGAL AGENTS

Invasive fungal disease represents a growing medical problem due to several factors, with special emphasis on the increasing implementation of treatments that suppress the immune system, with the consequent failure or inability to fight off opportunistic fungi. Currently available treatments for deep-tissue fungal infections have low survival rates, and are associated with a range of serious complications along with side-effects. Drug resistance is also a very significant issue, with high impact on treatment availability for critical patients. The following is a short description of 3 novel therapeutic options to this significant clinical problem, presented at the ASM Microbe 2017.

NP339 (Novamycin®) is a broad spectrum antimicrobial, active against clinically challenging pathogenic yeast and filamentous fungi. Its mechanism of action consists on charge-charge dependent interaction between NP339 (cationic) and fungal cell membrane (anionic) leading to membrane perturbation and lysis. This mode of action rapidly neutralizes both non-metabolizing and metabolically active fungi. It is important to highlight that NP339 also prevents biofilm formation. Novamycin® represents a potential antifungal peptide that rapidly kills target pathogens in such a way as to minimize the chances of drug resistance, especially on yeast and probably not that much on some filamentous fungi.

VL-2397 represents a potentially new class of antifungal agents. Invasive aspergillosis is the starting point of the development roadmap. This antifungal agent presents a novel mechanism of action; it occurs via Sit1 (a non-existent transporter in mammalian cells), so its activity results from effect on an intracellular target (Denning D, Science 2015). Phase 1 clinical trial showed that VL-2397 appears to be safe and well tolerated with favorable plasma PK profiles in healthy subjects.

The investigational product is currently in a Phase 2 trial. The multicenter, open label randomized clinical study, will compare the efficacy and safety of VL-2397 to standard treatment for invasive aspergillosis in acute leukemia patients and recipients of allogeneic hematopoietic cell transplant. The pri-

mary endpoint of the trial is all-cause mortality at 4 weeks and the key secondary endpoint is all-cause mortality at 6 weeks. The trial will be conducted at selected sites in North America, Europe and Asia. (Sean M. Sullivan, June 03 2017).

On the other hand, VT-1161 is a potent and selective, orally administered inhibitor of fungal CYP51, which has successfully completed Phase 2b clinical trials for the treatment of recurrent vulvovaginal candidiasis (RVVC) and onychomycosis. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane. It has demonstrated unprecedented efficacy in RVVC patients, with as low as 0% recurrence rates through 48 weeks. This treatment option seems to be safe and well tolerated, with an adverse event profile similar to placebo. These results suggest that VT-1161 may be a promising agent to treat RVVC, a condition associated with a very high burden of disease and for which there are no approved therapies; besides VT-1161 may avoid the side effects that limit the use of current oral antifungal therapies, such as liver toxicity and drug-drug interactions. (Sun-AAID LB21).

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Highlights from 9th Conference on HIV Science from International AIDS Society

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INTRODUCTION

This congress is one of the main forums to raise awareness of the latest advances and developments in the field of HIV infection. It is difficult to summarize the amount of information presented, but we believe the most relevant pieces could be categorized in three sections: epidemiological aspects of infection in Africa, safety of antiretroviral treatment during pregnancy, and data on new drugs and antiretroviral treatment strategies.

Epidemiological data on the HIV situation in Africa. In the study published by Nkambule et al. [1] the prevalence, incidence and degree of viral suppression in a national representative sample of people older than 15 years in Swaziland was analyzed. This is one of the countries with the worst HIV epidemic in sub-Saharan Africa. The study included 10.934 subjects. Since 2011, there has been an important improvement in the collection of epidemiological data, getting close to the 90-90-90 UNAIDS objectives, which means 90% of people with HIV are diagnosed, 90% are on antiretroviral treatment and 90% are under viral suppression. Published data from 2016 show that in Swaziland, 84.7% are diagnosed, 87.4% are in treatment and 91.9% are suppressed. The HIV prevalence infection over this period of time has changed in this country from 32.1% to 30.5% (without significant differences); the incidence has decreased from 2.5% to 1.4% (reduction of 44%, p 0.012); and patients with viral suppression following treatment has increased from 34.8% to 71.3% (increase above 100%, p < 0.001). These data are extraordinarily positive and suggest that with the generalization of treatment, the HIV epidemic in this area of the world can be partially controlled.

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Data on maternal-fetal transmission and safety of antiretroviral treatment during pregnancy. Almost everywhere in the world, drugs included in the first treatment lines are a combination of two nucleoside reverse transcriptase inhibitors (lamivudine [3TC] or emtricitabine [FTC] plus tenofovir [TDF], mainly), together with a third drug that in most cases is a non-nucleoside reverse transcriptase inhibitor (especially nevirapine or efavirenz). Efavirenz (EFV) is a very safe and effective drug, whose main toxicity relates to the central nervous system (dizziness and insomnia during the first weeks of treatment). In animal experimental studies, the use of EFV is associated with the development of congenital defects [2]. However, these data have not been confirmed in registries of women with HIV who continued taking this drug during pregnancy. In general, EFV is the most widely used drug in pregnant women but data of potential toxicity make it reasonable to look for better tolerated regimes. In this IAS congress the results of the Tsepamo [3] study have been presented; this is a prospective observational study carried out in Botswana which included 5.438 pregnant women, and which analyzed the risks of toxicity associated with the use of EFV / FTC / TDF and dolutegravir (DTG) together with FTC/TDF. In the study the complications related to treatment were low, quite similar to those observed in general population (around 10% of pregnancies) and there were no differences between both types of treatment in adverse effects during pregnancy (adjusted relative risk [aRR] 1.0 (95% CI 0.9-1.1), neonatal death (aRR 0.9 IC95% 0.6-1.5), prematurity (aRR 1.0, IC95% 0 , 8-1.1) or low birth weight (aRR 1.0 95% CI 0.9-1.2). These results suggest that EFV neonatal toxicity is very low, which reinforces that it is a safe drug in these circumstances. DTG, however, has the same low toxicity and is well tolerated in this situation, so it can be considered an alternative drug to the EFV, when circumstances do not allow for it to be used.

New antiretroviral drugs. Bictegravir (BIC) is a new integrase inhibitor that has been studied in combination with

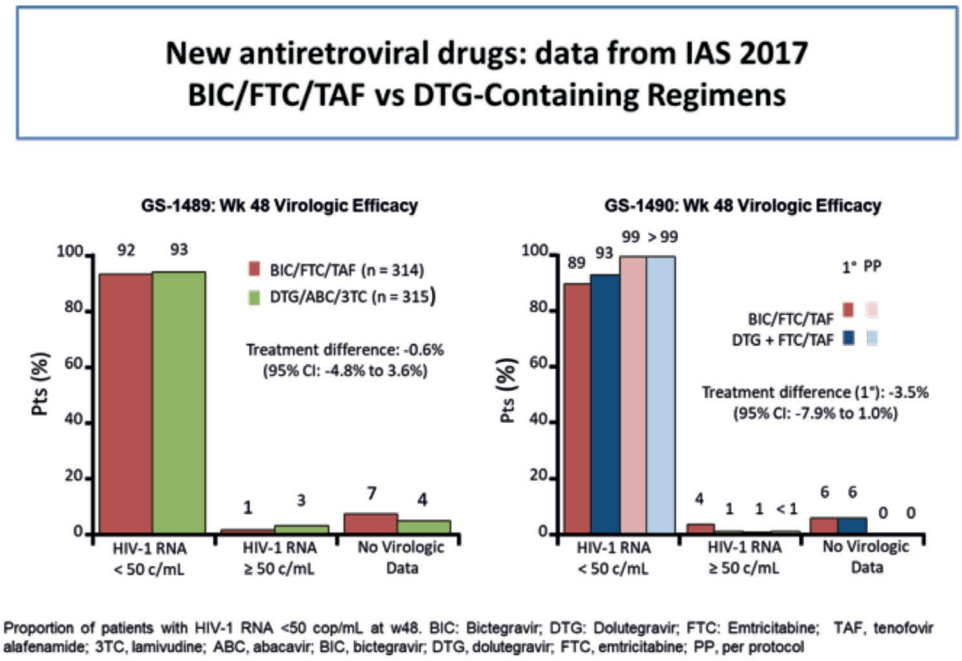

Figura 1 | **New antiretroviral drugs. Data from IAS 2017. Bictegravir/TAF/FTC vs Dolutegravir-containing regimens . Adapted from Gallant J et al [4] and Sax PE. et al [5]**

tenofovir alafenamide (TAF) and FTC, in a single pill. It has the advantage of having a high genetic barrier to resistance. Its favorable pharmacokinetics allows once a day administration, and it does not require an enhancer. In this congress the results of two trials comparing BIC / TAF / FTC to DTG, which is the most modern inhibitor of integrase with very similar characteristics to BIC, have been presented. The GS-US1489 [4] trial is a double-blind study comparing BIC / TAF / FTC against DTG / abacavir (ABC) / 3TC in 630 naive patients; after 48 weeks of treatment there were no significant differences in the patients with undetectable viral load (<50 copies). The double-blind trial GS-US 1490 [5], (BIC / TAF / FTC compared to DTG plus TAF / FTC in 640 naive patients) confirmed that there were no significant differences between both arms. In both studies, the viral response rates were higher than 90% of the patients, and no viral failures or resistance mutations were detected. In the protocol analysis, more than 99% of the patients presented viral suppression at week 48 (figure 1). These magnificent results of BIC / TAF / FTC combination anticipate a very promising future for this treatment.

Darunavir/cobicistat/TAF/FTC. Darunavir (DRV) is a protease inhibitor (PI) that has been combined in a single pill along with cobicistat (COBI), TAF and FTC. Clinical trials results about this switching strategy with very good results were published. The Emerald study [6] is an open-label study that included 11.459 patients on PI treatment, who were randomized to continue with the same regimen or switch to DRV/COBI/TAF/FTC in a single pill. At 48 weeks, 95% of patients had viral suppression <50 copies, with no differences between the two arms; virological failures were below 1% with no differences between the two arms of the study and resistance mutations were not detected. In the TAF arm, patients developed an improvement in bone mineral density and a reduction in tubular toxicity markers compared to patients in the control arm. This new unique tablet composed of protease inhibitors has very positive levels of efficacy and safety.

Long-acting therapies cabotegravir/rilpivirine (CBG/RPV). Long-term treatments offer advantages over oral treatment that may be relevant for some patients. The most important is the improvement in compliance, since an intramuscular dose (IM) applied every 2 months could cover the whole treatment during this period. CBG/RPV is a drug combination administered parenterally that has been studied for a short time offering promising results. In the Latte-2 study [7], two doses of CBG / RPV were compared by IM route (every month and every 2 months) versus CBG + ABC / 3TC orally. In IAS 2017, the data for week 96 were published, showing the non-inferiority of both parental branches, compared to the VO; specifically, 87% of those assigned to CBG / RPV IM each month had HIV-1 RNA < 50 copies /ml in week 96, compared to 94% of those treated with CBG / RPV IM every 2 months and 84% of those treated with CBG + ABC / 3TC orally. 30% of the patients who received IM treatment had adverse effects related to the injection, mostly mild. 88% of the patients assigned to IM treatments were very satisfied with this medication compared to 43% of those who received oral treatment. The results of the phase III trials are expected because these therapeutic strategies can be very interesting for many patients.

Dual therapies (dolutegravir/rilpivirine) as a simplification strategy. Treatments based on two drugs may be useful in some patients as a simplification to diminish drug toxicity. At IAS 2017 the results of the Sword Clinical Trial [8] (combination of dolutegravir and rilpivirine, DTG/RPV) have been published. It included 1,024 patients with HIV infection who had suppressed viral load and who were randomized to receive either DTG/RPV or to continue with their basic treatment. At 48 weeks, 95% of the patients continued to be under viral suppression. Significant improvement in bone mineral density was observed, since 73% of patients received TDF at the time of study inclusion.

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Highlights on bacterial infections in ID Week 2017

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The ID Week held in San Diego seemed to me to be an extraordinary Congress of which some figures can illustrate its magnitude. There were 287 different sessions, of which 30 were oral abstract sessions and 97 poster sessions. The poster sessions were visited by guided groups and 32 different rounds were held. The total number of abstracts were 2,451. In addition to this original material, there were multiple educational sessions featuring 83 symposia, 10 keynote lectures, 15 interactive sessions and 30 sessions of meet the professor. In general, the Congress has had a very educational character with many sessions dedicated to Stewardship and a lot of didactic technology, including several aspects of telemedicine. It was a congress that, in my opinion, greatly facilitated the recycling of professionals. If there is to be any catch in it, again in my personal opinion, the congress had little microbiology and little basic science and minimal participation of Europeans.

One of the most interesting areas was the review of antimicrobials currently in phase three of development that included drugs such as delafloxacin, Intravenous fosfomycin, cefiderocol, plazomycin, omadacycline, eravacycline, lefamulin, iclaprim, meropenem/vaborbactam and imipenem/relebactam.

In the field of Gram-positive infections, the 112 presentations dedicated to *Staphylococcus aureus* with abstractcs dedicated to the economic comparison of ceftarolin and daptomycin in MRSA bacteremias, the use of linezolid in vancomycin-resistant enterococcal bacteremia, the activity of tedizolid against *S. aureus* isolates and data on its future use in patients with cystic fibrosis were highlighted. A highlighted study was the one in which a validation of the Spanish NOVA score was presented to evaluate the risk of endocarditis in patients with Enterococcal bacteremia in 1,117 patients. In the field of *Enterococcus* bacteremia, I was struck by an abstract that showed the very high frequency of colonic lesions in patients with *Enterococcus* bacteremia of apparently unclear origin, demonstrating the need for colonoscopy in these patients.

Clostridium difficile and its infections motivated 147 communications or posters that were headed with an interesting controversy about the best way to make the diagnosis. Negative CRP in faeces is the best way to exclude the potential involvement of this micro-organism in a particular clinical picture. Several studies pointed to *C. difficile* toxigenic colonization as a high risk factor for developing clinical ICD. With a view to the indication of vaccines or the use of monoclonal antibodies, some Big Data studies have pointed to the usefulness of this technology in selecting populations at risk that merit the use of these resources. Several posters with data derived from the MODIFY studies showed that the population with a low blood antitoxin B titre is particularly prone to recurrence. In addition, the proportion of patients with chronic kidney failure was 28% and have an increased risk of recurrence. Studies with typing with complete genome show that only 40% of *C. difficile* isolates have an identical predecessor among the cases that occur in a hospital environment and that the transmissibility of these microorganisms is lower than previously imagined. The use of lyophilized faecal microbiota was shown to be as effective as other forms of faecal therapy. Without leaving the *C. difficile* area, data were presented on ribaxamase, an oral β-lactamase capable of breaking down β-lactams that reach the intestinal lumen, thus protecting against microbiota alterations that lead to *C. difficile* diarrhea.

In Gram-negatives, the 27 communications dedicated to ceftolozano-tazobactam were highlighted, of which 4 were dedicated to data on clinical use and included data on dosing in patients with cystic fibrosis and in children between 12 and 18 years of age, as well as the excellent activity against isolates of *Pseudomonas aeruginosa*. The combination ceftazidime-avibactam also merited several communications including the results of a clinical trial comparing with meropenem in nosocomial pneumonia, whether or not associated with mechanical ventilation.

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In the area of bacterial infection, I was particularly interested in the study of the convenience of studying the nasal carrier stage in a population that is going to undergo herniorrhaphy and the impact of decolonization. The data suggest the desirability of such an approach. The longest series of post-surgical medication I know of was also published in a group of 63,764 patients undergoing coronary bypass surgery, 1% of whom suffered this complication.

Syphilis continues to complicate the lives of humans and an abstract was presented with data on the evolution of ocular syphilis in a population of several centers in Montreal.

These are just some of the many interesting facts of a congress that I clearly think is more than advisable for all of us.

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Changes in bacterial hospital epidemiology

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ABSTRACT

Antibiotics' use and prescription requires a profound review, as their inadequate administration has been one of the main forces leading to resistance as a result of overuse and misuse. Resistance is particularly challenging in nosocomial environments in which there has been a gradual change in bacterial epidemiology owing to the continuous increase of multi-drug-resistant isolates, which imply a threat to prevent and cure infections. Expertise at the time of using antibiotics, development of new diagnostic tools and the possibility of having new antimicrobials are required to stay ahead of evolving resistance. Moreover, surveillance is also relevant to monitor antimicrobial resistance.

Key words: multi-drug-resistance, nosocomial environment, resistance prevalence

Cambios en la epidemiología bacteriana en el hospital

RESUMEN

El uso y la prescripción de antibióticos requiere una revisión profunda ya que la administración inadecuada ha sido una de las causas más importantes de la resistencia, como resultado del empleo excesivo e inadecuado de los mismos. La resistencia es un problema particularmente desafiante en el ambiente hospitalario en el cual ha habido un cambio gradual de la epidemiología bacteriana debido al aumento continuo de aislamientos multirresistentes, lo que implica una amenaza para la prevención y curación de las infecciones. El conocimiento adecuado de los antibióticos, el desarrollo de nuevas técnicas de diagnóstico y la posibilidad de disponer de nuevos antimicrobianos son necesarios para adelantarnos a la evolución de la resistencia. Asimismo, los estudios de vigilancia son relevantes para la monitorización de la resistencia a los antimicrobianos.

Palabras clave: multirresistencia, ambiente hospitalario, prevalencia de resistencia

INTRODUCTION

The concept of "One Health" is a worldwide strategy promoted by health authorities that recognizes the link between human and animal health, as well as the ecosystem integrity in the fight again antimicrobial resistance [1]. Achievement of this goal requires the collaboration between physicians, veterinarians, and environmental specialists. Moreover, it requires also the involvement of health authorities, politicians and population in general [2].

An outstanding part of this "One health" action is devoted to fight against antimicrobial resistance through the joint of educational, communications, surveillances, new diagnostic methods implementation as well as prevention and control of antimicrobial resistance emergence and dispersion. With this aim, various regional, national and international action plans have been proposed and are nowadays in progress. The European Union (EU) directs efforts to shape a worldwide strategy to fight against resistance, as this is an interconnected problem requiring coordinated global control measures [3].

The High-level Meeting on Antimicrobial Resistance that was held on 2016 at the General Assembly of the United Nations posed the problem and the possible solutions to be addressed on this respect by all member states. The most outstanding among them obviously coincide with those measures proposed by the EU and can be summarized as the mandatory sanitation, hygiene and infection control as well as the easy of access to better antimicrobials worldwide, the education and

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implementation of stewardship programmes and the research in new molecules and strategies of treatment as well as the availability of rapid diagnostic tools [4].

FACING THE PROBLEM OF MULTIDRUG RESISTANT BACTERIA

Incidence of hospital-acquired infection varies among countries and even more, among different hospitals from the same country, as complexity of large hospitals is inevitable high, requiring strict control measures of infection containment, which is not always successful. Moreover, not infrequently, patients colonized or infected with nosocomial pathogens are transferred between countries, regions and health care centres, and this may have consequences for the care of patients [5].

Nosocomial infection affects huge number of patients globally, increasing mortality rate and financial losses significantly. Prevalence of nosocomial infections varies according to the economic status with estimated ranges of 3.5-12% in high-income countries whereas it varies between 5.7% and 19.1% in middle and low-income ones [6]. According to the Study of Prevalence of Nosocomial Infections in Spain (EPINE, "Estudio de Prevalencia de las Infecciones Nosocomiales en España"), in 2017, the overall incidence of nosocomial infections was 7.7% (313 hospitals surveyed and 61,673 patients). Percentages of the most frequent nosocomial infections were as follows: surgical, 26%, urinary, 20%; respiratory, 19%; bacteraemia and catheter-related infection, 16%; and other infections, 19%.

Microbiology results reported by EPINE in 2017 are shown in table 1**.** When compared the prevalent organisms reported in this study with those considered by the WHO [7], life-threatening species with growing antimicrobial resistance, a strong coincidence exists between both sources (table 2). Moreover, most of them belong to the so-called ESKAPE group. This acronym was initially defined by Rice [8] to gather those species particularly resistant that currently cause the majority of hospital infections and effectively "escape" the effects of currently used antibacterial drugs. Nowadays, the organisms included are vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus,* multi-drug-resistant *Klebsiella pneumoniae,* multi-drug-resistant *Acinetobacter baumannii,* fluoroquinolone-resistant *Pseudomonas aeruginosa*, and multi-drug-resistant *Enterobacter* spp. The epidemiologic variations observed in the last years highlighted the need of a change from the initial proposed acronym ESKAPE to ESCAPE to accommodate *Clostridium difficile* (*E. faecium*, *S. aureus*, *C. difficile*, *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae) [9].

Microorganisms included in the Critical Category are particularly threatening in hospitals, nursing homes, and among patients whose care requires ventilators and blood

Table 1 Bacterial pathogens depicted according to their relative frequency (Higher than 1%) in nosocomial infections in Spain (EPINE-2017)

MICROORGANISM	N	Percentage
Escherichia coli	712	15.8
Pseudomonas aeruginosa	434	9.6
Staphylococcus aureus	434	9.6
Klebsiella pneumoniae	359	8.0
Enterococcus faecalis	310	6.9
Staphylococcus epidermidis	284	6.3
Enterococcus faecium	182	4.03
Enterobacter cloacae	146	3.2
Proteus mirabilis	146	3.2
Clostridium difficile	108	2.4
Acinetobacter baumannii	81	1.8
Morganella morganii	61	1.3
Stenotrophomonas maltophilia	61	1.3
Serratia marcescens	59	1.3
Klebsiella oxytoca	52	1.1
Enterobacter aerogenes	47	1.0

Table 2 WHO classification of "Priority pathogens" for which new antibiotics are urgently needed

PRIORITY	MAIN RESISTANCE FEATURE
Critical	
Pseudomonas aeruginosa	Carbapenems
Acinetobacter baumannii	Carbapenems
Multi-drug-resistant *Enterobacteriaceae*	Carbapenems and 3rd. gen. cephalosporins
High	
Staphylococcus aureus	Methicillin, intermediate vancomycin
Enterococcus faecium	Vancomycin
Helicobacter pylori	Clarithromycin
Campylobacter spp.	Fluoroquinolones
Salmonella enterica	Fluoroquinolones
Neisseria gonorrhoeae	3rd. gen. cephalosporins, fluoroquinolones
Medium	
Streptococcus pneumoniae	Penicillin
Haemophilus influenzae	Ampicillin
Shigella spp.	Fluoroquinolones

catheters. They can cause severe infections such as bloodstream infections and pneumonia. "High" and "Medium" categories include an important number of various species with increasingly drug-resistance trend. Surprisingly, *Clostridium difficile* is not included in the WHO list although the epidemiology of *C. difficile* infections (CDI) has dramatically changed since the early 2000s, with an increasing incidence and severity across Europe. This is partly due to the emergence and rapid worldwide spread of the hypervirulent and epidemic PCR ribotype 027 [10]. Moreover, *Mycobacterium tuberculosis*, whose resistance to traditional treatment is growing, particularly in some countries, was excluded in this list because it is subject of other control programmes conducted by this organization.

Concerning antimicrobial use, when comparing previous and present data from EPINE, the prevalence of patients receiving antibiotics rose from 36.8% in 2000 to 46.1% in 2017, entailing almost 10% increase in a decade. This augment of the antimicrobial load in the hospital environment inevitably leads to an increase in pressure and selection of resistant variants that tend to persist in the nosocomial setting, able to emerge when both patient's and environment's conditions are favourable.

THE PERFECT STORM: EPIDEMIOLOGY OF INVASIVE ISOLATES IN EUROPEAN UNION (EU) HOSPITALS, THE CASE OF SPAIN

For most bacterial species reported to the EARS-net (2016), resistance percentages varied across Europe, being generally higher in southern than in northern countries; as a consequence, mean values are reported. Evolution of resistance (2013-2016) in the most significant pathogens associated with nosocomial infections are briefly exposed [11].

Carbapenemase-producing *Klebsiella pneumoniae*. The highest EU mean resistance percentage in 2016 was reported for third-generation cephalosporins (25.7%, the majority due to ESBLs), followed by fluoroquinolones (24.6%), aminoglycosides (19.0%) and carbapenems (6.1%). A total of 2.4% of all reported *K. pneumoniae* isolates in EU were resistant to colistin. The majority of these were reported from Greece and Italy but a low number of isolates had been tested against this antimicrobial, so these findings should be interpreted with caution and may not be representative for Europe as a whole. However, emergence of colistin resistance mediated by plasmid-mediated *mcr-1* to *mcr-7* genes is undoubtedly alarming, not only due to the rapid and ease of its dispersion but to its presence in highly drug-resistant Enterobacteriaceae isolates harbouring plasmids encoding carbapenemase genes [12,13]. Dispersion of carbapenemase producing *K. pneumoniae* has been associated with high-risk clones.

Carbapenemase-producing *Escherichia coli*. Combined resistance to fluoroquinolones, third-generation cephalosporins (mainly due to ESBLs) and aminoglycosides increased significantly during the period 2013-2016. Up till 2016, a low percentage of 0.1% of carbapenems resistance was reported. However, there is a growing threat to resistance to these compounds in *E. coli* mediated by a range of carbapenemases. The increasing prevalence of carbapenemase producing *E. coli* depict a complex alarming situation as this organism might be responsible for carbapenemase transmission to other Enterobaceriaceae as occurred with CTX-M enzymes.

Multidrug-resistant *Pseudomonas aeruginosa*. Resistance to many important antimicrobial groups including carbapenems was common in *P. aeruginosa* in many European countries in 2016. Moreover, *P. aeruginosa* is intrinsically resistant to several antimicrobials complicating treatment of serious infections. However, a slight decreased (13% to 10.3%) in combined resistance including piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems was recorded. However, in Spain, this situation is different and combined resistance rose from 12.2% to 14.5%. In the case of carbapenems, 17.6% of isolates were resistant in 2013 while this value was of 21.4% in 2016.

Multidrug-resistant *Acinetobacter baumannii*. In this species, mean percentage for combined resistance to fluoroquinolones, aminoglycosides and carbapenems was 31.7% in 2016 being of 44.3% among Spanish isolates. In the case of carbapenem-resistant *A. baumannii,* reports published in 2016 concluded that the epidemiological situation in parts of Europe has worsened in the past years, like Spain, in which reported resistance for invasive isolates is higher than 50%. Although reports on colistin resistance are scarce (probably due to difficulties in reliable susceptibility testing), in some countries like Greece and Italy percentage of resistance varies between 2-4%.

Methicillin-resistant *Staphylococcus aureus* (MRSA). A decrease in percentage of MRSA occurred in the EU between 2013-2016. Despite this trend (18.1% *vs.*13.75%), a percentage above 25% remains in one third of the reporting countries including Spain, in which this resistance rose from 22.6% (2013) to 25.8% (2016). Methicillin resistance coded solely by the *mecA* gene along many years has recently "added" to new genes, *mecC*, a variant of *mecA,* and also *mecB,* a plasmid-encoded transferable gene previously found in *Macrococcus caseolyticus* [14,15]. *mecB* gene is present in a multi-drug-resistance transferable plasmid that harbours genes encoding additional resistances. The presence of plasmid-encoded methicillin resistance in *S. aureus* in a healthcare setting reveals a novel level of risk of the transfer of broad β-lactam resistance in staphylococci [15].

Vancomycin-resistant *Enterococcus faecium*. Global European percentages varied from 9% (2013) to 11.8% (2016). In Spain, these figures are low 0.9% (2013) and 2.1% (2016).

Either *vanB* or *vanA* may account for this resistance profile and their distribution is variable depending on local epidemiological landscape [16]. The dispersion of the CC17 in many hospitals is responsible for the added resistance to ampicillin and penicillin in these isolates. The spectrum is worsened by the less activity of daptomycin in this enterococcal species, as the MIC_{90} is 4 mg/L.

CONCLUSIONS

EARS-Net data for 2016 show that antimicrobial resistance remains a serious threat to public health in Europe. For invasive bacterial infections, treatment with effective antimicrobial agents is necessary to reduce the risk of a fatal outcome. The high percentages of isolates with resistance to key antimicrobial groups reported from many countries are therefore of great concern. In addition to increased mortality rates, multi-drug-resistant Gram- negative infections are also associated with a higher economic burden due to their greater severity and increased resource utilization; longer hospital stays and increased hospital and antimicrobial therapy costs. Prudent antimicrobial use, comprehensive infection prevention and control strategies are the key of effective intervention to prevent the selection and transmission of bacteria resistant to antimicrobial agents.

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A comprehensive approach for the patient with *Clostridium difficile* infection

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ABSTRACT

During the last decade there have been many changes and advances in the research on *Clostridium difficile* infection (CDI). We have improved diagnostic and therapeutic tools and, at the same time, we have learned that the CDI implies, especially in the most vulnerable patients, an important morbidity. CDI has traditionally been undervalued and it is widely dispersed in hospitals. Surely, there is inertness in its management and there are also broad areas of improvement. If we add to this the high cost of the new drugs and the practical difficulties to implement the faecal microbiota transplant, we realize that we may not be taking full advantage of all the opportunities to improve patient's outcomes. The implementation of policies that favour the supervision of all CDI cases by an expert in infectious diseases will contribute to a better global management of this important disease.

Key words: *Clostridium difficile*, recurrence, clinical prediction tools, management.

Valoración integral del paciente con infección por *Clostridium difficile*

RESUMEN

Durante la última década ha habido muchos cambios y avances en la investigación sobre la infección por Clostridium difficile (ICD). Han mejorado las herramientas diagnósticas y el tratamiento de la enfermedad al mismo tiempo que hemos aprendido que la ICD implica, especialmente en los pacientes más vulnerables, una importante morbilidad. La ICD ha sido tradicionalmente infravalorada y su atención médica está muy dispersa en los hospitales. Seguramente, hay una gran inercia en el manejo de esta enfermedad y, por ello, amplias áreas de mejora. Si a lo anterior sumamos el alto coste de los nuevos medicamentos y las dificultades prácticas para implementar el trasplante de microbiota fecal, es fácil concluir que no aprovechemos al máximo todas las oportunidades para mejorar los resultados clínicos que padecen ICD. La implementación de políticas que favorezcan la supervisión de todos los casos de ICD por parte de un experto en enfermedades infecciosas contribuirá a un mejor manejo global de esta importante enfermedad.

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The absence, for decades, of new drugs and advances in diagnostic techniques has kept *Clostridium difficile* infection (CDI) in a secondary plane of the infectious diseases. Traditionally, there was hardly more debate than the one involving the decision of using vancomycin or metronidazole to treat patients (and surprisingly for favouring the less efficacious drug). Moreover, recurrences of the disease were also accepted as unavoidable facts. In summary, the management of CDI has been very conservative and, in some way, too passive.

However, the scenario of the disease has changed radically in recent years due to three factors: we are witnessing an increase in the incidence derived from new hypervirulent strains [1], new faster and more sensitive diagnostic techniques have arrived [2] and, finally, we have very relevant new therapies that allow to modify the natural history of the disease [3-5]. These diagnostic and therapeutic novelties pose new challenges and confront microbiologists and infectious diseases specialists with new questions and complex decisions. How should the new more expensive diagnostic techniques be implemented in the laboratories? How to interpret the results of these more sensitive techniques? Which patients should be offered (or not) new treatments that are more effective but much more expensive?

Table 1 **Clinical prediction tools for CDI recurrence**

Author	Methods	Model	AUC	Accuracy	Applicability
Hu [11]	Prospective cohort (63 cases) External validation (89 cases)	Age >65, Antibiotics after CDI, Horn index.	0.83	77%	Low[1]
Eyre [12]	Retrospective cohort (1678 cases) No external validation	Age (60-69; 70-79;>80) Type of admission, previous MRSA, previous Gastroenterology ward admission, level of CRP, admission with CDI	ND	ND	Low
Hebert [13]	Retrospective cohort (829 cases) No external validation	Age, fluoroquinolones, ICU admission, cefalosporins, metronidazole or PBI after CDI	0.70	ND	Low[1]
Zilberberg.[14]	Retrospective cohort (4196 cases) Not external validation	Age, >2 hospital admissions 2 months before, community onset-health care associated, high risk antibiotics at DI onset, FQ at CDI onset, acid secretion suppression, ICU admission	0.64	ND	Low
D'Agostino [15]	Retrospective cohort (922 cases) Not external validation	Age >75, >10 stool, Creatinine >1.2 mg/dL, previous episode, not fidaxomicin	0.64	ND	High
LaBarbera [16]	Random forest -machine learning algorithm- (198 cases) No external validation	Not applicable	0.83	66%	Low
Viswesh [17]	Prospective cohort (340 cases). Not external validation	CDI at admission, nosocomial CDI, T^{a}>37.8 ^{o}C at admission, Leukocyte >15.000/ uL at admission, abdominal distension	0.72	ND	High
Cobo [18]	Prospective cohort (274 cases) External validation (185 cases)	Age (70-80; >80), previous CDI episode, free toxin+, diarrhoea day +5 of treatment	0,72	75%	High

[1]**Some variables are not available during the period of treatment (e.g. antibiotics after CDI)**

It is clear that we can currently improve the management of patients with CDI. In this article we will review three relevant aspects, such as the importance of correctly interpreting the tests to avoid overdiagnosis, how to identify patients with high risk of recurrence and how to better manage the disease globally in health institutions.

DECISION TO TREAT MATTERS MUCH MORE THAN ONE COULD THINK

The incorporation of techniques based on molecular biology for the diagnosis of CDI currently allows us to diagnose virtually all cases, since these techniques reach a sensitivity of almost 100% and may be available within a few hours from the collection of the sample. As recommended by scientific societies, most centres carry out diagnostic algorithms in two or three steps, which implies that some patients are eventually diagnosed by molecular techniques (NAAT), while the detection of free toxin is negative (NAAT+/ TOX-), and on the contrary in others the toxin is detected directly in the patient's stool (TOX+). At present we know there is evidence that there are differences between these two populations and, although there are still controversies, in general we can say that globally there are fewer severe cases and less symptomatic disease (and therefore more colonization) in the NAAT+/TOX- than in the TOX + [6,7].

Vancomycin is practically not absorbed and, therefore, adverse effects due to its administration are not expected. This idea, together with the assumption that its administration could eradicate *C.difficile* from the intestine of patients at risk, may lead many physicians to not raise many doubts about the treatment once it receives the result of the toxigenic *C.difficile* detection in the stool of their patients. There are at least two important harmful consequences of this attitude. First, several studies have shown that vancomycin (and also metronidazole) exerts a profound effect on the diversity of the human intestinal microbiota and, in fact, favours colonization by enterococci, by antibiotic resistant Enterobacteriaceae [8]. We also know that this colonization precedes many infections. Therefore, an unnecessary administration of vancomycin may be confronting new risks to frail patients. Secondly, the decision to treat implies the diagnosis of a CDI episode. This means

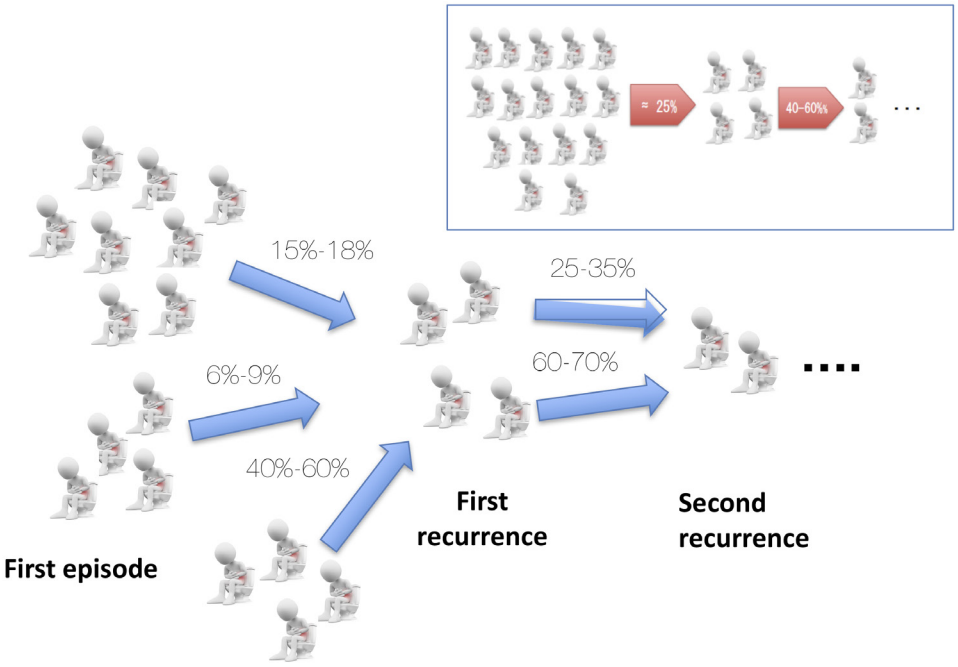

Figure 1 **The upper figure is true: globally the patients in the first episode present a lower risk than the patients in the second episode. However, this does not mean that all patients in the first episode (or in the second) have the same risk of recurrence. The knowledge of risk factors and predictive models can allow us to identify subpopulations of higher and lower risk.**

that if the patient were to be diagnosed (correctly or not) of a new episode, probably the use of expensive or sophisticated treatments would be unnecessarily considered. Indeed, in a recent study, a reference centre for faecal microbiota transplantation reported that after evaluating the cases referred by other physicians, they considered that 25% of the patients had been diagnosed incorrectly of recurrent CDI [9].

WHO ARE THE PATIENTS AT HIGH RISK OF RECURRENCE?

Until recently we could hardly modify the risk of recurrence of patients. At best, we could recommend them to avoid the use of antibiotics and proton pump inhibitors if they were not strictly necessary. However, today we have new antibiotics (fidaxomicin) and a monoclonal antibody (bezlotoxumab) that allow us to significantly reduce recurrences, changing the natural history of the disease. They would be used routinely in most cases if it were not for its high cost. An efficient use of these resources requires the ability to select patients with a high risk so that the number of patients needed to treat is substantially reduced.

Multiple investigations have shown several recurrence risk factors, some of which are repeated consistently [10]. These include the age over 65 years, continued use of PPIs or antibiotics, previous treatment with quinolones, kidney failure and history of previous episodes of CDI. But we should not forget others such as inflammatory bowel disease, having an enteral tube or severe immunosuppression. As all these factors can coexist and interact, the mere knowledge of the risk factors is not enough to establish, when evaluating a given patient, the specific risk of recurrence.

A more useful approach are clinical prediction tools, and even more recently the use of big data and machine learning systems (table1) [11-18]. Important limitations of these tools should be recognized. Only two of the models have been validated externally and not all the tools proposed are easy to apply in real practice. In addition, the accuracy of the models is not very high. However, they allow to discern subgroups of high and low risk reasonably well, and show us that the risk for patients in the first episode can vary widely and, in some cases, can be even higher than the risk established for patients in the second episode (figure 1)

As an example, in a recently published study we followed a prospective cohort of 274 patients of which 25% had recurrence. By means of multivariate analysis we were able to generate a clinical prediction rule with a precision of 0.75 and AUC 0.72. The included variables were age (with two different rang-

es), the history of a previous episode of CDI, having a positive toxin determination in faeces and a slow response defined by continuing diarrhea after 5 days of treatment [18]. Considering this model, for example, an 85-year-old patient in a severe first episode diagnosed with a positive toxin test and who shows a slow response, would have a risk of recurrent CDI greater than 50%, and in any case higher than a 68-year-old patient in his second episode diagnosed by PCR that shows a rapid response.

Not only risk assessment of recurrence but also an evaluation of potential consequences of CDI recurrence should be addressed. For example a recent report has shown that haematological patients on chemotherapy that present CDI recurrence suffer significantly more delays in the planned chemotherapy than patients without CDI recurrences [19].

Clinical guidelines usually arrange the recommendations for the treatment of CDI depending on the number of the episode and its severity. However, this approach could be excessively rigid for patients with a high risk of recurrence or with serious potential repercussions of it. In short, surely we should progress towards more individualized treatments.

CAN WE IMPROVE THE CARE OF PATIENTS WITH CDI?

CDI has been an undervalued disease for decades. One of the problems in its management – and it is not new for some nosocomial infections- lies in the wide distribution of the disease within the hospitals. We have calculated that the last 800 CDI cases in our institution have been attended by more than 25 different surgical and medical services and more than 100 different physicians. The potential consequences of such dispersion are variability in clinical management, lack of expertise to manage severe cases, lack of continuity in the medical care of patients with recurrent CDI, and difficult access to new drugs and therapies.

There exist some experiences showing benefits of "CDI stewardships" or CDI bundles [20] imitating other similar positive experiences such as the well-known effect of the supervision of *S. aureus* bacteremia by experts in infectious diseases.

In our opinion, supervision by an expert of all CDI cases diagnosed by the laboratory could improve the following points:

1) Avoiding treatments of merely colonized patients

2) Early detection of severe cases that require urgent evaluation by the surgeon

3) Favouring early access of patients at high risk of recurrence to new treatments

4) Serving as a reference physician for the management of patients with multiple recurrences, facilitating accessibility and rapid diagnosis

5) Supervising the inappropriate administration of antibiotics and PPIs to patients with recent diagnosis of CDI

Ideally, such a program should be coordinated with a reinforcement of infection control policies and education of health professionals on the mechanisms of transmission of CDI and the importance of judicious use of antibiotics.

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Top-ten papers in fungal infection (2015-2017)

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ABSTRACT

We have clustered the published articles in fungal infection between 2016 and 2017 in four categories. First, the emergence of *Candida auris* as a nosocomial pathogen associated to high antifungal resistance and high mortality. Second, the growing importance of fungal infections associated to the use of biologic therapies. Third, the approval of isavuconazole for the treatment of filamentous fungi and dymorphic mycoses with positive results and less side effects. And finally, a mix of other important news regarding empiric therapy, fluconazole toxicity and difficult-to-treat fungal infections.

Key Words: Fungal infection; Treatment; Biologic therapies.

Los mejores artículos sobre infección fúngica

RESUMEN

Hemos agrupado los artículos publicados sobre infección fúngica entre 2016 y 2017 en cuatro categorías. Primero, la emergencia de *Candida auris* como un patógeno nosocomial asociado a alta resistencia a antifúngicos y alta mortalidad. Segundo, la creciente importancia de las infecciones fúngicas asociadas al uso de terapias biológicas. Tercero, la aprobación de isavuconazol para el tratamiento de los hongos filamentosos y las micosis por hongos dimórficos con buenos resultados y menos efectos adversos. Y por último, una combinación de otras noticias importantes en cuanto a terapia empírica, toxicidad del fluconazol e infecciones fúngicas difíciles de tratar.

Palabras clave: Infección fúngica; Tratamiento; Terapias biológicas

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INTRODUCTION

In order to inform of novelties in fungal infections, we have revised the published articles dating between 2016 and 2017 regarding this topic from clinical, bedside and treatment points-of-view. We have classified the most relevant articles into the following groups: i) Characteristics of *Candida auris* infection; ii) Fungal infections in patients treated with biologic therapies; iii) News in antifungal treatment; iv) Mix of interesting news.

CHARACTERISTICS OF *C. AURIS* INFECTION

C. auris is an emergent pathogen fungus that represents a big challenge for identification. Moreover, infection control measures when *C. auris* infection is diagnosed are mandatory.

First of all, we will comment on the article by Vallabhaneni et al [1], describing the first seven cases of *C. auris* infection reported in the United States. This paper shows us some important findings. First, whole genome sequencing showed that isolates from patients admitted to the same hospital were nearly identical, suggesting the possibility of a nosocomial outbreak. Additionally, the authors demonstrated that patients were colonized by *C. auris* for a long time after the initial infection and there existed multiple contaminated surfaces in the healthcare environment, potentially spreading throughout.

Later, Ruiz-Gaitán et al [2] reported the first four cases of one of the most important hospital outbreaks occurring in Europe (Valencia, Spain). Importantly, the authors showed how they initially misidentified the *C. auris* species. Investigation into the species continued due to the presence of a high-level resistance to fluconazole and voriconazole. The researchers characterized *C. auris* infection by genetic methods. The overall mortality was high (50%).

To finish this section, we will comment on the important paper of Lockhart et al [3], that describes 41 patients with *C.*

auris infection from 3 different continents. Whole-genome sequencing showed 4 different strains emerging simultaneously worldwide. High mortality rate (around 60%) and high antifungal resistance were found. All but four strains were highly resistant to fluconazole but very few were resistant to itraconazole and posaconazole (suggesting an efflux-pump mechanism related to fluconazole resistance); 7% were resistant to echinocandins and almost 50% were resistant to amphotericin B. Two strains were pan-fungal resistant.

FUNGAL INFECTIONS IN PATIENTS TREATED WITH BIOLOGIC THERAPIES

Patients receiving biologic therapies is a new, rising category of immunosuppressed hosts, about whom many questions about prophylaxis, treatment and general management are still unresolved.

Furthermore, an increasing evidence shows that different effects on the immune system could be associated with an increased risk of infections. For example, a randomized trial to evaluate the effectiveness of a monoclonal antibody against interleukin-17 demonstrated a huge efficacy of the therapy for psoriasis control, but noteworthily, the most important side effect of this drug was the *Candida* infection [4]. Also in this regard, different reports show an increased incidence of fungal infections in patients receiving tirosin kinase inhibitors and other biologic therapies [5–7] an antigen consistently expressed on B-lineage acute lymphoblastic leukaemia cells. We aimed to confirm the activity and safety profile of blinatumomab for acute lymphoblastic leukaemia. Methods: In a multicentre, single-arm, open-label phase 2 study, we enrolled adult patients with Philadelphia-chromosome-negative, primary refractory or relapsed (first relapse within 12 months of first remission, relapse within 12 months after allogeneic haemopoietic stem-cell transplantation [HSCT], or no response to or relapse after first salvage therapy or beyond, raising an international concern about this topic [8].

NEWS IN ANTIFUNGAL TREATMENT

In the coming years, new antifungals are going to be available, such as new echinocandins with better pharmacokinetic/pharmacodynamic profile. Nowadays, a new azole has been approved to fight fungal infections: Isavuconazole. Furthermore, in the future, new immunological approaches would be useful in improving patients' outcomes.

With regards to isavuconazole, we will first comment about the articles, by which this new antifungal was approved for the treatment of aspergillosis and mucormycosis [9,10]. First, the SECURE was a phase 3, randomized-controlled, non-inferiority trial comparing isavuconazole versus voriconazole for the treatment of invasive filamentous fungi. In this study, isavuconazole was non-inferior in mortality at 6 and 12 weeks, with significantly less side effects [9]. Secondly, the single-arm, open-label trial by Marty et al [10] assessed the efficacy and safety of isavuconazole for treatment of mucormycosis. All-cause mortality was reported to be around 40%. Additionally, a matched case control analysis was performed, using patients from the FungiScope Registry who had been treated with amphotericin B. No differences were found in terms of efficacy, with the arm of isavuconazole showing also less side effects. However, is important to point out that doses and surgical approach were not uniform in the patients from the FungiScope and a previous study with high doses liposomal amphotericin B and a high percentage of surgery showed higher response rates [11].

Meanwhile, an open-label, non-randomized phase 3 trial was conducted to evaluate the efficacy and safety of isavuconazole treatment in management of some dimorphic mycoses [12]. In this paper, rates of successful outcomes were like those previously described with other antifungals treatments, that is, isavuconazole has an acceptable safety profile and in turn, a possibly useful alternative in these patients.

The final paper of this section is an experimental mice model by Lionakis et al [13] based on the blockade of chemokine receptor CCR1. The authors were able to demonstrate that immunocompetent *Candida*-infected mice treated with this inhibitor improved its survival, decreased kidney fungal burden and provided protection from renal tissue injury.

MIX OF INTERESTING NEWS

The last group of articles revolve around three important aspects: empiric therapy, fluconazole toxicity, and difficult-to-treat fungal infections.

First, we will talk about the article of Timsit et al [14]. This is a multicenter double-blind and placebo-controlled study evaluating the empiric role of micafungin treatment in patients with ICU-acquired sepsis who had *Candida* colonization and multiple organ failure. A high number of patients were included (n=260) and randomized for receiving either placebo or micafungin, with high adherence to the intervention. No differences were found per prognosis between the control and intervention group. One possible limitation of this study is that they described a very low rate of patients being at high risk for invasive candidiasis (gastrointenstinal surgery, parenteral nutrition...).

Secondly, we will comment on a nationwide cohort study in Denmark with more than 1,400,000 pregnant women in order to assess a possible association between oral fluconazole use in pregnancy and the risk of spontaneous abortion and stillbirth [15]. Oral fluconazole-exposed pregnancies were compared with up to 4 unexposed pregnancies matched on propensity score, maternal age, calendar year, and gestational age. Importantly, the authors strongly related the use of oral fluconazole with spontaneous abortions. No association was found with stillbirths, but the number of stillbirths was quite low in the whole cohort. These results firmly preclude the use of oral fluconazole in this population.

Finally, Cuervo et al conducted a multicenter study in 9

Spanish hospitals to evaluate the role of echinocandins in patients with candidemia caused by a urinary tract source [16]. Although the current guidelines preclude the use of echinocandins for this kind of candidemia, these authors demonstrated via the use of a propensity score approach that early initial echinocandin therapy was not associated with clinical failure. The only factor related with improved outcome was the drainage of the urine focus.

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Fungal biofilms: From bench to bedside

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ABSTRACT

Biofilms cause recurrent invasive infections that are difficult to eradicate because of their high resistance to antimicrobials and host defence mechanisms. Fungal biofilm-related infections are associated with high mortality rates. Although current guidelines recommend catheter removal for catheter-related bloodstream infections due to *Candida* species, several studies have shown that the efficacy of the antifungal lock technique. The use of combinations of antifungal agents may improve the management of biofilm-related fungal infections and prevent the emergence of resistance associated with monotherapy. Since the presence of mixed bacterial-fungal biofilm infections is very prevalent, a combination of antibacterial and antifungal agents should be considered.

Key words: *Candida*, biofilm, antifungal, lock technique

Biopelículas fúngicas: Del laboratorio a la práctica clínica

RESUMEN

Las infecciones relacionadas con biopelículas fúngicas se asocian con altas tasas de mortalidad. La infección asociada a catéteres son un ejemplo. Aunque las guías actuales recomiendan la retirada del catéter para tratar estas infecciones, varios estudios han demostrado la eficacia de la técnica de sellado antifúngico. El uso de combinaciones de agentes antifúngicos puede mejorar el pronóstico de las infecciones fúngicas relacionadas con biopelículas y prevenir la aparición de resistencias. Las infecciones asociadas a biopelículas mixtas (bacteria-hongo) son cada vez más frecuentes y requieren de un abordaje específico para conseguir su erradicación.

Palabras clave: *Candida*, biofilm, antifúngicos, técnica de sellado

INTRODUCTION

A biofilm is a community of microorganisms embedded in a self-produced matrix of extracellular polymeric substance (EPS) that can adhere to biotic or abiotic surfaces and so facilitate survival in a large number of environments, including medical devices. Biofilm-associated organisms are responsible for more than 60% of all microbial infections in humans. Biofilms cause recurrent invasive infections that are difficult to eradicate because of their high resistance to antimicrobial treatments and host defence mechanisms and their excellent ability to adhere to biomaterials [1].

In many cases, colonization precedes infection. The main involved microorganisms are usually commensal flora, including bacteria and fungi. Gram-positive cocci, mainly coagulase-negative staphylococci, are involved in more than 70% of foreign body related infections. The fungal pathogen most commonly associated with biofilm infections is *Candida albicans* and the resulting infection is associated with a high mortality. Other biofilm-forming *Candida* species include *C. parapsilosis*, *C. tropicalis*, *C. krusei* and *C. glabrata*. *Cryptococcus neoformans*, *Coccidioides immitis*, *Aspergillus* spp., *Fusarium* spp., *Blastoschizomyces capitatus*, *Malassezia pachydermatis*, *Pneumocystis* spp.,*Trichosporon asahii*, *Rhizopus* spp. and *Rhizomucor* spp. are also described as causative agents of biofilm-related fungal infections [2]. Common sites for fungal infections are the oral cavity, lungs (mainly in ventilated patients), burn wounds, the lower reproductive tract, skin and intravascular catheters, the gastrointestinal tract and at insertion sites of urinary catheters.

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C. albicans biofilm, which is the fungal biofilm model that has been best studied, comprises two main kinds of cell: small oval yeast-form cells (blastospores) and long tubular hyphal cells. The formation of *C. albicans* biofilms involves four stages: First, *adherence* of the yeast-form cells to a substrate; second, initiation and proliferation of biofilm formation, in which the yeast cells proliferate across the surface producing elongated projections that grow into filamentous forms containing hyphae and pseudohyphae (*proliferation* stage); third, *maturation* into a complex, structured biofilm, in which the cells encased in the extracellular matrix display increased drug resistance. Finally, *dispersal* of the yeast-form cells from the biofilm to colonize the surrounding environment [3].

Studies of the regulation of fungal biofilm formation have gradually become much more important in recent years, with the discovery of the genes and regulatory mechanisms involved and the identification of molecules with potential quorum-sensing functions in biofilm maturation. Many biofilm genes encode cell wall proteins that can play a direct role in cell-substrate or cell-cell adherence. Other genes involved in biofilm formation encode predicted transcription factors or protein kinases. Several alcohol dehydrogenase and aryl-alcohol dehydrogenase genes also have an impact on biofilm formation [4].

An important factor involved in biofilm formation is the nature of the material to which the microbial cells adhere. In the case of human infections, this means the chemical composition of materials used in medical devices. *Candida* spp. has the ability to form biofilms on the surfaces of a variety of medical devices, such as those made of polymethyl methacrylate (PMMA), silicone, elastomer, polyurethane, polyvinyl chloride, polypropylene and polystyrene. Other important factors involved in biofilm formation include the conditioning film, *Candida* morphogenesis, the fungal strain, bacterial competition/cooperation and the location of the implanted medical device [5].

CLINICAL RELEVANCE OF BIOFILM FORMATION

Candida spp. can cause severe disseminated disease associated with high mortality, particularly in patients with implanted medical devices or compromised immune systems. Wisplinghoff et al. analyzed data from a prospective nationwide surveillance study carried out over a 7-year period in US hospitals that included 24,179 cases of nosocomial bloodstream infection (BSI) [6]. *Candida* spp., isolated mainly from patients being cared for in intensive care units (ICU), was the fourth causal agent detected (9%) and was associated with the highest crude mortality rate (39.2%). The mortality rate was even higher in patients admitted to the ICU (47.1%). *C. albicans* was the most common yeast isolated (54%), followed by *C. glabrata* (19%), *C. parapsilosis* (11%) and *C. tropicalis* (11%). The crude mortality rate was lowest for *C. albicans* infection (37%) and highest for *C. krusei* infection (59%). The rate of *Candida* spp. isolated from blood cultures increased from 8% to 12% over the 7-year period. In another study, Tumbarello et al. evaluated the risk factors for mortality in 294 hospitalized patients with *Candida* BSI, specifically testing to determine whether biofilm formation was a risk factor associated with a worse evolution [7]. More than 25% of these patients were infected by biofilm-forming isolates. The mortality rate in patients with BSI due to biofilm-positive isolates (70%) was significantly higher than in those due to biofilm-negative isolates (45.7%) and infection by biofilm-forming *Candida* spp. was an independent risk factor for mortality.

BIOFILMS AND ANTIFUNGAL RESISTANCE

Biofilms are often associated with high-level antimicrobial resistance. *Candida* spp. can develope antimicrobial resistance during treatment with antifungals via expression of the following mechanisms: changes in the fungal cell wall that reduce the absorption of the antifungal agent; changes in drug-target affinity; and increased overexpression of the membrane transport proteins that facilitate the efflux of antifungal drugs. The major genes that contribute to drug resistance are those encoding transport proteins that efflux multiple drugs. The *Candida* genome has gene families that encode the ATP-dependent transporters (ABC) and major facilitators (MDR), the CDR and MDR genes, respectively, which are regulated during the formation and development of the biofilm [5]. Nonetheless, the main survival mechanisms of biofilm cells against antifungals are the physical barrier to the entry of antifungals created by the extracellular matrix, and the increased cell density, enhanced stress response and decreased metabolic activity shown by the biofilm cells. In fact, biofilm-forming cells are able to survive in the presence of high concentrations of antimicrobial agents, even though the same cells are susceptible in the planktonic phase. This phenomenon is known as recalcitrance [8].

LOCAL ANTIFUNGAL TREATMENT

For catheter-related BSI due to *Candida* species, the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection by Mermel et al. recommend catheter removal and treatment with antifungal therapy for 14 days after the first negative blood culture [9]. However, the antifungal lock technique has been considered an option in selected patients (haemodynamically stable patients with severe coagulopathy or with limited or no other options for vascular access) [8]. Several studies have shown the efficacy of antifungal agents as catheter lock solutions. Cateau et al investigated *in vitro* the optimal antifungal lock treatment details against *C. albicans* biofilms. Equinocandins significantly reduced the metabolic activity of *C. albicans*, suggesting that they could be good candidates for use in catheter lock solutions [10]. Successful results have also been obtained in animal models, with a catheter salvage rate of more than 80% (54/64), mainly using amphotericin B lipid complex as the antifungal agent. There are a limited number of published case reports describing the use of antifungal lock therapy in

various patient populations. Amphotericin B deoxycholate was the most commonly used antifungal agent, with a catheter salvage rate of 76.9% (10/13), followed by liposomal amphotericin associated with a 60% catheter salvage rate (3/5) [11]. *In vitro* studies showed anidulafungin to be a promising option in antifungal lock therapy [12].

OTHER THERAPEUTIC OPTIONS

The use of combinations of antifungal agents may improve the management of biofilm-related fungal infections and prevent the emergence of resistance associated with monotherapy. Some in vitro studies analyzed the activity of various antifungal combinations against *Candida* biofilms. The best results were obtained with the amphotericin B/posaconazole combination (synergistic against 100% of strains tested) compared with other combinations that yielded indifferent (amphotericin B/caspofungin, amphotericin B/fluconazole, fluconazole/caspofungin), or even antagonistic effects (voriconazole/micafungin) [13]. Promising results were also obtained from *in vitro* studies that analysed the activity of amphotericin B in combination with antibiotics (rifampicin or clarithromycin) against *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. krusei* and *C. tropicalis* biofilms [14].

MIXED BIOFILMS

Since the human microbiota is diverse and includes a variety of bacteria and fungi, multispecies or polymicrobial biofilms are often found. In the vast majority of cases, *C. albicans* interacts with bacteria in the specific niche where the biofilm infection originates, such as *S. epidermidis* in the skin or *Streptococcus* spp. in the oral cavity. Bacterial cells can bind directly to *C.* albicans hyphal cells in the biofilm, or they can be linked through the mediation of other factors such as fungal adhesion proteins, hyphal wall proteins or regulators of transcription. The bacterial-fungal interaction may be synergistic, with the mixed biofilm offering one or both species physical protection or enhancing the virulence of both species compared with the monomicrobial infection, or it can have an inhibitory effect, causing the destruction of one of the microbial agents [3]. In addition, the susceptibility of the microorganisms in a mixed biofilm may be higher than in the monomicrobial counterpart. These complex interactions are likely to have significant clinical implications, so that understanding the mechanisms involved in adhesion and signalling in fungal–bacterial interactions could lead to the development of novel therapeutic strategies for impeding microbial colonization and the development of polymicrobial disease [15].

CONCLUDING REMARKS

Biofilm infections are difficult to eradicate because of their high resistance to antimicrobial treatments, mainly due to efflux pumps and persister cells forming within biofilms. Not all antifungals have the same activity against *Candida* biofilms. Since the biofilm-forming capacity of *Candida* is a determinant of mortality, better knowledge of this form of fungal development is necessary to develop new therapeutic strategies. Further studies are needed to understand the complexity of polymicrobial biofilm infections and interspecies interactions.

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Practical Decalogue in the management of sepsis

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ABSTRACT

Sepsis is a complex entity where there are still many controversies regarding diagnosis and therapeutic management. The present article pretends to review the recently published in relation to these disagreements and contains a proposal of practical approach to the infected patient.

Decálogo práctico en el manejo de la sepsis

RESUMEN

La sepsis es una entidad compleja donde existen aún múltiples controversias en cuanto al diagnostico y el manejo terapéutico. El presente artículo pretende hace una revisión de lo publicado recientemente en relación con estas polémicas y ofrece una propuesta de aproximación práctica al paciente infectado.

INTRODUCTION

Sepsis is an increasingly frequent entity with high morbidity and mortality [1]. One of the mean characteristics is that initial decisions can condition the patient's prognosis. Therefore, we must be clear about what to do and when to do it. For this reason, there are numerous published guidelines that address this complex syndrome. However, and despite the attempt to standardize the care, there are still many controversies in both diagnostic and prognostic or therapeutic aspects, key issues that we will review next.

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DIAGNOSIS

The diagnosis of sepsis requires first of all the presence of infection, which is not always easy to determine. Klein Klouwenberg et al [2] showed that among patients admitted to the Intensive Care Unit (ICU) for sepsis, 13% did not present an infectious disease and in the 30% it was only possible. The study concludes that the diagnosis of sepsis at admission corresponds poorly with the final diagnosis. Other studies carried out on necropsies have shown in patients admitted to the ICU that the clinical and anatomopathological diagnoses do not match with certain frequency, with type I errors being the most frequent. These errors are characterized because if it had knowledge of the true diagnosis, the therapeutic attitude would have changed. The discrepancy between the clinical diagnosis and that of the necropsy occurs in both senses. That is, patients diagnosed clinically for an infectious process did not present it at necropsy and infection was demonstrated in patients without this clinical diagnosis [3].

The complex physiopathology of the septic syndrome may justify the difficulties in establishing the clinical diagnosis (table 1) [4]. Another aspect that makes it difficult is the progressive increase in the age of the attended population, and the fact that this one more frequently presents important comorbidity or immunosuppression, aspects that make that the clinical and analytical manifestations of our patients are often atypical [5].

RISK STRATIFICATION

As a result of the publication of the definitions of Sepsis-3, an important controversy about the effectiveness of quick sequential organ failure assessment (qSOFA) as a screening tool to detect patients with suspected sepsis has been established in the literature. In the last year, new studies have been published that evaluate the prognostic accuracy of the qSOFA and other scales such as the National Early Warning

Table 1 Signs in sepsis and mimics

	Sepsis	Other etiologies
Tissue damage	Production of pro and anti-inflammatories	Injuries, hypoxia, ischemia, toxins
Hemodynamic effects (initial stages)	Decrease in peripheral resistances, with increased cardiac output and tachycardia	Distributive shock: anaphylaxis, pancreatitis, spinal cord injuries
Hemodynamic effects (late stages)	Increase in peripheral resistances, decrease in cardiac output, colder peripheral limbs with poor capillary refill time	Hipovolemic shock
Laboratory data	Leucocytosis with left deviation Coagulopathy C reactive protein Procalcitonin Lactic	Physiological stress Systemic inflammation
Fever	Cardinal sign of infection Related to cytokines in the hipothalamus	Problems in the elderly, immunosuppressed, and patients with biological therapies.

Adapted from Long B, et al. J Emerg Med. 2017;52:34-42

Score (NEWS) or Systemic Inflammatory Response Syndrome (SIRS) in the initial evaluation of the patient with suspected infection [6]. Several systematic reviews and meta-analyzes have recently been published. Serafim et al (7] show that the prognostic accuracy is greater for the qSOFA while SIRS shows a better sensitivity for infection diagnosis. So, they advocate a combination of both and not to establish an exclusive competition between them.

In the meta-analysis of Fernando SM et al [8] it is striking that among the 38 studies evaluated, the sensitivity and specificity of qSOFA ranges from 0.98-0.12 and 0.19-0.96, respectively. Likewise, the sensitivity and specificity of SIRS ranges from 0.99-0.51 and from 0.05-0.68, respectively. This shows that probably the populations studied are very heterogeneous or that the clinical stage of the infection is different, because otherwise the dispersion of the reported results can not be explained. Another meta-analysis and systematic review of the literature shows that Early Warning Score (EWS) are not sufficiently accurate to rule in or rule out mortality in patients with sepsis, based on the evidence available, which is generally poor quality [9].

Last, other remarkable study is the one that evaluates the qSOFA depending on the source of infection, showing that an area under the curve (AUC) of 0.841 in urinary tract infection vs. 0.722 in the respiratory track infections (p <0,001), showing the influence that can have the site of infection in their prognostic accuracy [10].

The problem to establish the prognosis is given because the infection is a dynamic process and in the studies the variables are measured on a one-time. Probably the best strategy will be determined by the monitoring of these scales, observing their deterioration in the first hours in order to identify the patient with high risk of poor outcome [11].

TREATMENT

Multiple articles show that complying with the 3-hour bundles (measuring lactate, taking blood cultures and administering antibiotics] leads to a reduction in mortality in patients with sepsis or septic shock. A more rapid completion of a 3-hour bundle of sepsis care and quick administration of antibiotics, but not quick completion of an initial bolus of intravenous fluids, were associated with lower risk-adjusted in-hospital mortality [12].

However, studies that assess adherence to these recommendations show that only 25% of physicians achieve this goal. Among patients with severe sepsis or septic shock receiving antimicrobials in the emergency department, door-to-antimicrobial times varied five-fold among treating physicians. Given the association between antimicrobial delay and mortality, interventions to reduce physician variation in antimicrobial initiation are likely indicated [13].

Studies show that Emergency Department crowding was significantly associated with lower compliance with the entire resuscitation bundle and decreased likelihood of the timely implementation of the bundle elements [14]. The structured care by a code for the patient with sepsis has led in multiple publications to a significant reduction in the mortality [15].

However, even in this, there is controversy. SSC guidelines affirm that administration of antimicrobials should begin as soon as possible after sepsis identification and within the first hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence). However, the IDSA, fearing that this will lead to overprescription of antibiotics in uninfected population or the overuse of broad spectrum antimicrobials, and considering that this recommendation is supported only by observational studies, recommends that in patients with

sepsis (without shock), is better to completed studies in order to determine if infection is the responsible of the patient´s clinical manifestations, and once it is confirmed start antibiotic treatment as soon as possible [16].

Finally, SSC guidelines suggest that in septic shock, combined treatment with 2 antimicrobials, both active against the microorganism, may be useful. It is recommended to continue until the clinical improvement or resolution of the infection, independently of the microbiological results of susceptibility. The IDSA, on the contrary, states that there are no solid data to support these recommendations. The evidence would support the empirical use of two active agents against Gram-negative bacilli for the empirical treatment in septic shock in order to increase the chances of administering at least one active agent, but once the susceptibility is known available data suggest that there is no evidence to support the treatment continuation with two agents [16].

A recent Spanish study corroborates that there is no difference, once the susceptibility is known, between maintaining biotherapy or establishing monotherapy with the active agent [17]. However, it is important to note that this study excludes neutropenic patients and infection by *Pseudomonas* spp, where future studies are required.

DECALOGUE

The discrepancy in the results showed by the different studies that address the problem of sepsis is given because they try to label different profile patients with the same definitions and therapeutic attitudes. Sepsis is an heterogeneous syndrome secondary to different etiologies and with a wide range of severity. The clinical presentation, the prognosis and the therapeutic approach will depend on the source of infection, the immunological situation of the host, age, comorbidity, and timing. Two patients can meet the definition of septic shock by requiring inotropes or having high lactic acid, but nevertheless have different age, comorbidity or site of infection. All these factors can conditionated the therapeutic approach or the outcome of the episode.

Kalil et al. [18] make a recommendation of approaching the infected patient based on 4 points: identify the site of the infection, source control, evaluate the immunological status of the host and establish whether it is in shock or not. The site of infection can conditionate the etiology and, therefore, the selection of the antimicrobial treatment. But it also has connotations in the prognosis since it is known that certain sources of infection, such as respiratory or abdominal, have higher mortality than others such as urinary tract infection [19]. The source control has been shown to be essential in improving the patient's prognosis and poor control is associated with increased mortality [20]. The immunological situation can condition the mortality and the etiology of the process. Therefore, it is necessary to know if the patient has a solid organ or hematopoietic cells transplant, cancer, chemotherapy, immunotherapy, HIV with less than 250 CD4, takes immunosuppressive medication or biological therapy, or receives chronic corticosteroid treatment [21]. Finally, the shock situation must be evaluated since it conditions a higher mortality. To the contribution of Kalil et al [18] we thought that the consideration of comorbidity should be added, since this will be related to higher mortality and have therapeutic implications. It is known that a Charlson index greater than 2 leads to an 10% excess of in-hospital mortality [22].

CONCLUSION

The approach based on the 5 previous points is valid to decide the therapeutic attitude. Severity stratification should be based not only on risk scores, which have a modest AUC around 0.75, but should be supported by biomarkers such as lactate or proadrenomodulin. Procalcitonin can be helpful in diagnosing infection.

In any case, when faced with an infection, cultures must be taken, antibiotics must be prescribed and the source control must be established, attitudes that must be completed as soon as possible regardless of the severity. Risk stratification is useful in establishing priorities.

Regarding the timing of antibiotic administration, in relation to the dispute between SSC and IDSA, we comment that both agree in what attitude must be follow against the shock. Regarding sepsis, we must consider that this definitions means that the patient has failure of at least two organs, and therefore it has an increase mortality of 10%. In this context, considering the risk-benefit evaluation, we think that early antibiotic administration must be done, especially considering that we are speaking of an initial moment where there can be great uncertainty both diagnostic and prognostic. We do not think that the administration of a single dose of antibiotic could condicionate a risk of serious adverse event on the patient or a significant modification on the ecosystem.

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Usefulness of biomarkers on infection management: with or without them?

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ABSTRACT

Infectious diseases are disorders caused by many different microorganisms that produce clinical conditions with a wide variation in patient-rated symptoms and severity. Therefore, different diagnostic and prognostic tools are needed to help make the most accurate decisions at each moment of patient´s care with suspected infection. This mini review will analyse how some biomarkers reduce the level of uncertainty in the making decision process at some phases of sepsis, including prompt identification of septic patients, early initiation of empiric broad-spectrum antimicrobials, regimen and duration.

Keywords: sepsis, biomarkers, procalcitonin, lactate, MR-ProADM

Utilidad de los biomarcadores en el manejo de la infección: ¿con o sin ellos?

RESUMEN

La patología infecciosa puede ser debida a microorganismos muy diferentes que producen cuadros clínicos con una expresividad muy variada tanto en los síntomas como en la gravedad. Por ello, se necesitan diferentes herramientas diagnósticas y pronósticas que ayuden a tomar las decisiones más adecuadas en cada momento de la atención a un paciente con sospecha de infección. En esta mini revisión se analizará cómo algunos biomarcadores disminuyen el nivel de incertidumbre en la toma de decisiones clínicas en algunas fases de la atención a la sepsis, como puede ser la propia identificación del paciente séptico, la necesidad de iniciar tratamiento antimicrobiano, el tipo y su duración.

Palabras clave: sepsis, biomarcador, procalcitonina, lactato, MR-ProADM

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INTRODUCTION

The response to infection is such a complex process that both in patients with compromised immune system, such as neutropenic or lymphopenic patients, or in those with exaggerated reaction, this dysregulated host response results in increased mortality rates. In fact, the update of sepsis definition considers the organ system dysfunction as a result of the host response [1].

In this interaction between the host and the pathogen, a large amount of molecules are released whose usefulness as biomarkers for screening, diagnosis, risk stratification or monitoring, has been studied with some contradictious results that have questioned its clinical application [2, 3].

Unfortunately, no biomarker in sepsis has proven to have 100% sensitivity and specificity at the same time to establish the diagnosis of an infectious cause in those who suffer some organic failure or indicate when antibiotic treatment should be started or stopped, but their use help to make these decisions with a smaller margin of error. Thus, the main utility of a biomarker is given by its likelihood ratios (LR). The LR (+) = Sensitivity / (1 - specificity) and the LR (-) = (1 - sensitivity) / Specificity. For example, when a sepsis is suspected, a useful biomarker will have a high LR (+), which increases the post-test probability supporting the clinical diagnosis.

In general it is considered that LR> 10 or <0.1 generate large and often conclusive changes from pretest to posttest probability LR of 5 - 10 and 0.1 - 0.2 produce moderate shifts in pre-test to post-test probability, LR of 2 - 5 and 0.5 - 0.2 generate small (but sometimes important) changes in probability and LR of 1 - 2 and 0.5 - 1 will alter the probability to a small and rarely important degree [4].

The use of some normograms allows to better visualize how diagnostic probability post-test improves with the use of biomarkers (figure 1) [5].

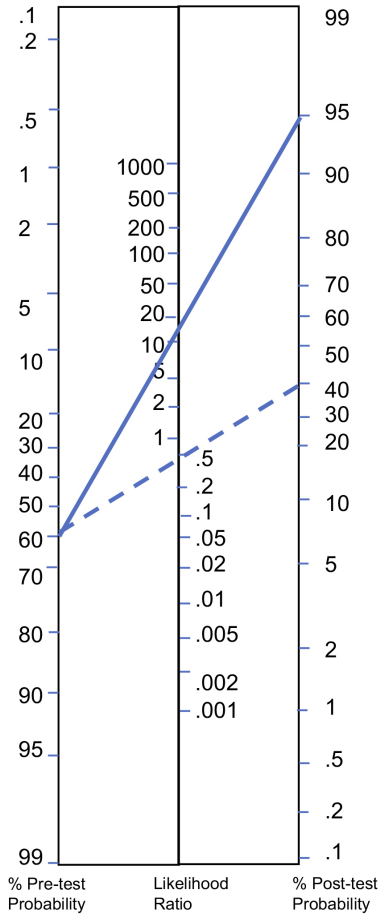

Figure 1 | **How interpret diagnostic test results. Adapted from Fagan[5].**

Let us suppose a biomarker as PCT has proved to have a LR(+) to diagnosing ventilator associated pneumonia (VAP) of 13.5 and a LR(-) of 0.55 for a cut-off level of 3 ng/mL[6]. When suspecting a patient is suffering from VAP because of clinical and radiographic findings with a probability of 60% if the PCT is > 3 ng/mL the probability of VAP will raise up to 95% (continuous line) while if PCT is < 3 ng/mL the probability will decrease to around 40% (dash line) which can help us to decide starting antibiotics or not.

The determination of some biomarkers such as lactate or procalcitonin (PCT) has been automated and become cheaper in recent years, which has extended its use and several studies establish their LR at levels that produce moderate and sometimes important changes in decision making [6-8].

This "mini" review will focus on analyzing how their knowledge helps reduce the level of uncertainty in clinical decision making and can help both identify more serious patients and make better use of antibiotics. A brief consideration will be given to what can be contributed by the mid regional pro-adrenomedullin (MR-ProADM), described more recently.

THE USEFULNESS OF BIOMARKERS IN THE STRATIFICATION OF SEVERITY

The early identification of septic patients is particularly important in those who are critically ill because the rapid establishment of resuscitation measures and administration of the appropriate antimicrobial reduce mortality [9].

Recent definitions of sepsis have attempted to improve the sensitivity and specificity of the systemic inflammatory response syndrome (SIRS) to identify patients at increased risk of death in the course of an infection, by proposing q-SOFA ≥ 2 in emergency department or SOFA score ≥ 2 in patients admitted in ICU as the definition of sepsis, in other words, the infection that causes organic dysfunction [10].

According to this, in order to identify septic patients among those suffering from infection, no biomarker would be needed in the emergency department, but they are essential in the ICU to calculate SOFA score. However, it is necessary to point out that in the publication that stablishes the basis for the latest definitions of sepsis [10], the mortality of patients with lactate ≥ 2 mmol/L and q-SOFA = 0 is similar to those who had q-SOFA ≥ 2 and lactate ≤ 2 mmol/L which shows the usefulness of this biomarker to identify patients whose clinical symptoms do not express the true severity so we consider that it is essential to determine lactate in cases of high suspicion of sepsis, which may be valid in a venous blood sample for this purpose. On the other hand, these same definitions state that in order to diagnose septic shock, the presence of hyperlactacidemia ≥ 2 mmol/L is necessary as well as the need to associate vasopressors to maintain the mean arterial pressure ≥ 65 mmHg after fluid resuscitation [11].

Therefore, obtaining lactate in the initial stages of suspected sepsis is crucial and should be re-measured because it has proven to be a useful tool to know if the clinical course of sepsis is being favorable [12].

PCT values, particularly in low ranges (0.5-2 ng/mL), are not very useful in identifying the most severe patients because of its little power of discrimination. However, very high values (> 10 ng/mL) suggest a significantly increased risk of sepsis and/or septic shock [13] and low values (< 0.2 ng/mL) practically rule out bacteraemia with a negative predictive value (NPV) > 98% [14] and consequently its determination will also help to make decisions in some cases. So a patient suffering from shock, very low levels of PCT (<0.2 ng/mL) confirmed 12 hours later, make a bacterial infection unlikely and require alternative diagnoses (viral infections, autoimmune conditions or other types of shock).

Recently, the role of MR-ProADM in emergency departments and critically ill patients has been studied as a marker of severity since it is more stable and its determinations more reproducible than adrenomedullin (ADM), a peptide hormone of the calcitonin family, produced by different tissues in response to physiological and pathological stress (including sepsis).

Specifically, MR-ProADM in patients older than 75 years treated in the emergency room for infection has shown to

have a predictive capacity of 30-day mortality much better than lactate, PCT or other biomarkers such as suPAR or PCR. A cut-off point of MR-ProADM > 2.07 mmol/L establishes a LR (+) of post-test death 19 times greater, which may alert of the need to admit these patients even if other biomarkers are normal. This same study shows that the predictive capacity of mortality at 30 days of the combined model qSOFA ≥ 2 and MR-proADM> 2.07 mmol/L reaches an area under the curve (AUC) of 0.87, higher than the predictive capacity of both variables separately [15].

In critical patients, it is also shown how in each range of severity measured by the SOFA scale (<6, from 7-12 and ≥ 13), increasing cut-off points of MR-ProADM (1.79, 3.25 and 5.58 mmol/L, respectively) have an AUC to predict mortality of 0.75 at 28 days [16].

In a study conducted by our hospital in 33 patients with sepsis or septic shock, in which 9 patients died with a median SOFA = 9 (RIQ: 7-10.5) for a cut-off point of MR-ProADM of 8.58 mmol/L, the AUC to predict mortality in ICU was 0.99, higher than lactate (0.80), PCT (0.72) and APACHE II score (0.82). Very interesting was also the finding that amongst patients with lactate ≤ 2 mmol/L, those who died had significantly higher levels of MR-ProADM (21.14 mmol/L) than the survivors (3.6 mmol/L), warning about the possible poor evolution of patients who apparently had a good prognosis based on lactate levels [17].

UTILITY OF BIOMARKERS TO GUIDE ANTIBIOTIC TREATMENT

Several studies have shown the importance of early administration of an adequate antibiotic treatment on the reduction of mortality, particularly in critically ill patients [18]. In this regard, if the patient is in septic shock, current biomarkers do not allow us waiting to start antibiotics until they rise up to a certain threshold level because, for instance PCT can take up to 6 hours to reach abnormal plasma levels, which would unjustifiably delay the start of treatment. However, in COPD patients with respiratory exacerbation or in cases of respiratory infection in primary care, the measurement of PCT avoids the overuse of antibiotics in a significant and safe way, compared to making decisions without knowing their value [19].

On the other hand, administering unnecessary or very prolonged antibiotics courses over time might be harmful to the patient [20], so limiting them for such period as is strictly necessary is mandatory. Some studies have shown that shorten duration treatments can be as effective and safe as longer ones [21, 22], but the fear that keeping them only for a few days decreases curation rates or increases recurrences, leads to unjustifiably prolonged treatments.

In this context, the PCT has proved useful because it becomes a tool that reduces the level of physician´s uncertainty when deciding to stop antibiotics.

Monitoring PCT levels allows shorten antibiotics in a significantly and safely way, particularly in cases of respiratory infection, an average of 2.5 days, even in critical patients [19, 23]. However, it is also important to take into account the limitations of PCT to make an adequate use of it. PCT is released to blood when monocytic cells adhere and interact with parenchymal cells as expression of systemic response to infection that might not occur in localized infections such as abscesses so PCT is not useful in those cases. The onset or duration of antibiotics in other serious infections such as endocarditis cannot be guided by PCT or other biomarker because it aims to "sterilize" the affected endocardial structure and that may require a long period of antibiotic treatment even though the PCT is normalized. Apart from that, the studies that have analyzed the role of PCT in guiding antibiotic duration have not included cases of endocarditis.

CONCLUSIONS

Biomarker measurements are necessary to determine SOFA score (bilirubin, creatinine, platelets) that rapidly identify patients with sepsis, especially in those admitted in ICU. Lactate and MR-proADM help identify septic patients at high risk of death, low PCT levels (<0.2 ng/mL) in cases of respiratory infection without organ dysfunction can prevent the onset of unnecessary antibiotics and its monitoring allows to shorten antimicrobial therapy without worsening the prognosis.

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Top-ten infections in onco-hematological patients (2015-2017)

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ABSTRACT

To choose the most relevant ten papers constitutes a challenge in several ways. We have elaborated this selection based on the papers we find to be most useful and ground-breaking for the clinician faced daily by the infectious problems in onco-hematological patients. The selection has been structured in four parts: bacterial infections, viral infections, fungal infections and infections related with new drugs in onco-hematological patients.

Key Words: bacterial infections, letermovir, aspergillosis.

Los mejores artículos de infecciones en el paciente oncohematológico

RESUMEN

Establecer que artículos son los "los top-ten" es difícil en varios aspectos. Hemos establecido esta selección basándonos en lo que hemos considerado más útil y novedoso en el conocimiento de la patología infecciosa en el paciente oncohematológico. Hemos estructurado la selección de los mismos en cuatro apartados: infección bacteriana, infección vírica, infección fúngica e infecciones relacionadas con los nuevos tratamientos en pacientes oncohematológicos.

Palabras Clave: infecciones bacterianas, letermovir, aspergilosis

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INTRODUCTION

During the last two years, a significative number of papers have been published on the field of infection in onco-hematological patients. To choose the most relevant ten papers constitutes a challenge in several ways. On one hand, the subjectivity of the author is unavoidable; an apparently less relevant article may, to the eyes the author, contribute with more fresh and useful ideas than one published in one of the top journals. Furthermore, on the other hand, there may be a relevant article that we forget to highlight.

Therefore, we have elaborated this selection based on the papers we find to be most useful and ground-breaking for the clinician faced daily by the infectious problems in onco-hematological patients. I apologize in advance if you do not find a paper you considered to be better or more relevant than the mentioned in the following selection.

This selection has been structured in four parts. First, we will comment the most innovative papers on bacterial infection and especially on the crucial topic of the development of antibiotic resistance in the onco-hematological patients and how to face this challenge. In a second part we will review an article on viral infection. In the third part we will review what is new in fungal infection, mainly on new risk populations and the raise in *Pneumocistis jirovecii* infections in onco-hematological patients. Finally, we will comment papers referring to new drugs for the management of onco-hematological diseases and how may they relate to the risk of infection. After each of the four sections, we will sum up the most relevant messages.

BACTERIAL INFECTIONS

The increasing number of infections caused by multi-drug resistant bacteria (MDRB) constitutes a major problem. This fact is of especial relevance in onco-hematological patients.

Given their disease and the treatments received, these patients often present significant immunosuppresion. This leads to numerous infections, thus requiring frequent and prolonged antibiotic exposure. A better knowledge on epidemiology of these infections and the development and implementation of measures to reduce antibiotic resistance are crucial.

In the first sudy, signed by Averbuch et [1] al all Gram-negative rod resistant (GNR) bacteremias occurring during 6 months post-HSCT (2/14–5/15) were prospectively collected and analyzed for rates and risk factors for resistance to fluoroquinolones, noncarbapenem anti-*Pseudomonas* β-lactams (noncarbapenems), carbapenems, and multidrug resistance. Sixty-five centres from 25 countries (mostly from Europe) participated in the study, reporting data on 655 GNR episodes and 704 pathogens in 591 patients (Enterobacteriaceae, 73%; nonfermentative rods, 24%; and 3% others). Half of GNRs were fluoroquinolone and noncarbapenem resistant; 18.5% carbapenem resistant; 35.2% multidrug resistant. e total resistance rates were higher in allo- geneic HSCT (allo-HSCT) vs. autologous HSCT (auto-HSCT) patients ($P < .001$) but similar in community-acquired infections. Noncarbapenem resistance and multidrug resistance were higher in auto-HSCT patients in centers providing vs. not providing fluoroquinolone prophylaxis ($P < 0.01$). Resistance rates were higher in southeast vs. northwest Europe and similar in children and adults. Non-*Klebsiella* Enterobacteriaceae were rarely carbapenem resistant. Multivariable analysis revealed resistance risk factors in allo-HSCT patients: fluoroquinolone resistance: adult, prolonged neutropenia, breakthrough on fluoroquinolones; noncarbapenem resistance: hospital-acquired infection, breakthrough on noncarbapenems or other antibiotics (excluding fluoroquinolones, noncarbapenems, carbapenems), donor type; carbapenem resistance: breakthrough on carbapenem, longer hospitalization, intensive care unit, previous other antibiotic therapy; multidrug resistance: longer hospitalization, breakthrough on β-lactam/β-lactamase inhibitors, and carbapenems. Inappropriate empiric therapy and mortality were signicantly more common in infections caused by resistant bacteria. In summary, the study questions the recommendation of fluoroquinolone prophylaxis and emphasizes the necessity of empiric antibiotic protocols based on the knowledge of resistances of each centre.

Gudiol et al [2], signed the second study where β-lactam/β-lactamase inhibitors (BLBLIs) were compared to carbapenems in two cohorts of hematological neutropenic patients with extended-spectrum- β-lactamase (ESBL) bloodstream infection (BSI): the empirical therapy cohort (174 patients) and the definitive therapy cohort (251 patients). The 30-day case fatality rates and other secondary outcomes were similar in the two therapy groups of the two cohorts and also in the propensity-matched cohorts. BLBLIs, if active *in vitro,* might be carbapenem- sparing alternatives for the treatment of BSI due to ESBLs in in high-risk hematological patients. This strategy may prove useful in limiting the spread of carbapenem resistance in this high-risk population.

The last study lead by Aguilar-Guisado et al [3], also from Spain, proposes a useful approach to reduce unnecessary exposure to antimicrobials and demonstrates that in high-risk patients with haematological malignancies and febrile neutropenia, empirical antibiotic therapy (EAT) can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. In four years, 157 episodes among 709 patients assessed for eligibility were randomized (78 to stop EAT after 72 h or more of apyrexia plus clinical recovery and 79 to the control group- when neutropenia was recovered). The mean number of EAT-free days was significantly higher in the experimental group than in the control group. One patient died in the experimental group (from hepatic veno-occlusive disease after an allogeneic haemopoietic stem-cell transplantation) and three died in the control group (one from multiorgan failure, one from invasive pulmonary aspergillosis, and one from a post-chemotherapy intestinal perforation).

VIRAL INFECTIONS

Cytomegalovirus (CMV) infection is a leading cause of illness and death in patients who have undergone allogeneic hematopoietic-cell transplantation. Over the past 20 years, clinicians have adopted a preemptive strategy. Thus, the development of safe and effective antiviral agents for CMV prophylaxis remains a major goal in transplantation.

Letermovir is an antiviral agent that inhibits CMV replication by binding to components of the terminase complex (UL51, UL56, or both), at a dose of 240 mg per day was highly effective in preventing CMV viremia after engraftment in a study published in 2014 [4]. Three years later, a phase 3, randomized, double-blind, placebo-controlled, superiority trial [5], resulted in a significantly lower risk of clinically significant CMV infection than placebo (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], P<0.001). The frequency and severity of adverse events were similar in the two groups. All-cause mortality at week 48 after transplantation was 20.9% among letermovir recipients and 25.5% among placebo recipients.

So, letermovir is a safe and effective drug for preventing CMV infection when used through day 100 after transplantation.

FUNGAL INFECTIONS

With the use of prophylaxis in high-risk hematological patients, the incidence of invasive aspergillosis (IA) has reduced in this group to below 3% [6]. On the other hand, with the use of new targeted or immunomodulatory drugs in the management of hematological malignancies an increase of IA is observed in patients considered of medium-low risk for fungal infection. We chose two articles, both of them from Livio Pagano's group focusing on the epidemiological changes based on the host.

In the first of them [7] is a unicentric, retrospective study that demonstrates that the new treatment strategies in lymphoproliferative disorders, including immunomodulating and

immunosuppressive agents, in addition to cytotoxic treatments and a more frequent application of autologous HSCT have caused an increased risk of IFIs among these patients. In this study, it seems particularly evident in MM and aggressive NHL patients, particularly when after HSCT. These changes in the epidemiology induced to modify the diagnostic workup for IFIs, now more frequent than in the past, in these patients. Although the incidence of IFI is below 5%, it is quite higher than the observed in these same patients 10 years before. Prospective studies are required to evaluate the potential usefulness of prophylaxis in these patient groups.

In the second study [8], the same group analyzed the current data regarding the epidemiology of and risk factors for IFIs in patients with HMs. The concept "non-static level of risk" for IFI is an interesting contribution. For instance, the risk of IFI could be low in patients at the time of diagnosis of the underlying hematological malignancy, while in the following months, the same patient could be considered at high risk in the case of non-responsiveness to the anti-neoplastic treatment. This review might offer a useful tool for designing future studies with the aim of optimizing the diagnostic procedures and therapeutic strategies for preventing and treating IFIs in patients with hematological malignancies.

Pneumocystis jiroveci (PJ) pneumonia is often diagnosed in onco-hematological patients undergoing chemotherapy or targeted therapies, frequently in combination with systemic steroids, that even in doses as low as the equivalent of 20 mg of prednisone a day for four weeks constitute and important risk factor [9]. In addition, PJ pneumonia in these patients presents distinctive features including higher mortality that may be aggravated by a later diagnosis and delayed treatment. On the other hand, indications for prophylaxis in oncological patients are not well established. ECIL guidelines have published three papers regarding epidemiology [10], treatment [11] and prophylaxis [12] of PJ pneumonia in hematological patients.

The following publications have provided more new data on this condition:

Takemoto et al [13], knowing that PJ can colonize in the lower airway and the air vesicles of some healthy individuals, analyzed the presence of PJ DNA with a nested PCR technique in bronchoalveolar lavage samples among outpatients during cancer chemotherapies and compared it with healthy controls. PJ DNA was detectable in 46% of specimens from cancer patients undergoing chemotherapy, and it was not significantly different among types of cancer and chemotherapy regimens. Detection of PJ DNA was lower among healthy non-smokers (20%) and high among healthy smokers (47%). They conclude that quit smoking and antibiotic prophylaxis may be necessary for cancer patients during chemotherapy.

In another study [14], as much as 27% of HIV-negative patients with PJ pneumonia presented with more than 200 /µL CD4+ lymphocytes, thus questioning this threshold for prophylaxis frequently used in HIV-positive patients.

As a personal opinion, due to the lack of solid clinical data, prophylaxis should be considered in patients receiving immunosuppressive treatment or chemotherapy, prolonged treatment of steroid and/or present persistent lymphopenia.

NEW TREATMENTS FOR THE MANAGEMENT OF ONCO-HEMATOLOGICAL DISEASES AND ITS IMPACT IN INFECTION

It is difficult to establish the risk of infection associated with a specific directed therapy due to the high number of confounders. In the first place, the onco-hematological condition itself is often associated with a higher number of infections, sometimes caused by opportunist pathogens. In the second place, treatments previously received by the patient may have a persistent effect on the immunitary system, even long after its interruption. Additionally, treatments administered for counteracting the adverse effects of these drugs, such as steroids, may further influence the risk of infection. Finally, a high number of patients receiving the treatment for a long time would be necessary, in conjunction with a significant number of infectious events, to establish an exact quantification of the risk.

An excellent review about risk of infectious complications in hemato-oncological patients treated with kinase inhibitors has been published by Reinwald et al [15] and is summarized in table 1. Recent publications have also focused its attention on ibrutinib and the increase in the incidence of fungal infections. Chamilos et al [16] presented opportunistic infections caused by *P. jirovecii* and *Cryptococcus neoformans,* ubiquitous airborne fungi in patients undergoing ibrutinib, with hematological cancers historically considered at low risk for IFI. The spectrum and severity of IFI observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. When aspergillosis occurred, it was more frequently observed within the first 4 months of treatment and affected more frequently in patients with central nervous system disease (primary central nervous system lymphoma), also receiving steroids (71%) and with refractory or relapsed malignancies (100% of cases).

The risk of infection among patients receiving immune checkpoint blockade is unknown. After reviewing medical records of 740 patients with melanoma who received immune checkpoint blockers, del Castillo et al [17] concluded that serious infection occurred in 54 patients (7.3%). The main risk factors were treatment with corticosteroids and/or infliximab to handle complications associated with immune related adverse events. Future studies will need to address the best approach to prevent infectious complications in these patients; cotrimoxazole prophylaxis is recommended when steroids are initiated. Aspergillosis and CMV enterocolitis need also to be in consideration when adverse events are treated with immunosupressors.

A French group [18] reviewed 2 cases of tuberculosis reported to French data-base of adverse events related with biological drugs in onco-hematological patients and 3 more pub-

Table 1 | **TK inhibidors, related infections and recommended prophylaxis. Modified from Reinwald M, et al [15].**

Pathway target inhibitor	Drugs	Indicative infections related to drug	Possible prophylaxis recommended
BCR-ABL	Imatinib, Dasatinib, Nilotinib, ponatinib, Bosutinib	HSV, CMV and Hepatitis reactivation, Neutropenic fever Upper Respiratoriy tract Infections	May be considered
BCR-Pathway-inhibitory	Ibrutinib, Idelalisib	Pneumonia Upper Respiratoriy tract Infections	May be considered
mTOR	Temsirolimus, Everolimus	VZV and HSV reactivation Invasive Aspergilosis *Pneumocystis jiroveci* Pneumonia	Aciclovir and Cotrimoxazole must be considered
JAK	Ruxolitinib, Tofactinib	None specific	Aciclovir and Cotrimoxazole must be considered
EGFR-ALK	Erlotinib, Gefitinib, Afatinib, Crizotenib, Ceritinib	Upper Respiratoriy tract Infections	None
Multikinase (esp VEGF)	Sorafenib, Sunitinib, Regorafenib, Axitinib, Pazopanib	VZV and HSV reactivation Invasive Aspergilosis *Pneumocystis jiroveci* Pneumonia	None
BRAF/MEK	Vemurafenib, Dabrafenib, Trametinib	None specific	None

lished. Although tuberculosis seems to be rare (1/1000 patients in France), its reactivation may be favored by the specific action of anti PD-1 agents. All patients should probably be tested with an IGRA before the initiation of anti PD-1 treatment, and closer collaboration between infectious disease specialists and oncologists is advisable.

We are at the beginning of a new period in medical history. New drugs are being added to the onco-hematological armamentarium every day, and most of them have an immunomodulatory effect. We must learn its negative effects on the defense against infections and how to manage them, we have to think about the infections in new populations of risk, and most important of all, we have to keep working in multidisciplinary teams for the benefit of our patients.

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Highlights in solid transplant infectious diseases 2015-2017

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ABSTRACT

Solid organ transplant recipients have an increased risk of developing infections due to the lifelong treatment with immunosuppressive drugs. Herein we review recent (2015-2017) and relevant published advances in the field of bacterial, viral and fungal-infections in this population. We also address the most up-to-date immunological assays that can predict the risk of infection. Finally, we review current guidelines and how they improve the usual clinical care.

Key words: Solid organ transplant; infectious diseases; immunosuppression

Lo más destacado en infección en trasplante de órgano sólido 2015-2017

RESUMEN

Los receptores de un trasplante de órgano sólido tienen un mayor riesgo de desarrollar infecciones secundario a la inmunosupresión. En este artículo, revisamos los avances más recientes (2015-2017) y significativos en el campo de las infecciones bacterianas, virales y fúngicas en esta población. También revisamos los estudios inmunológicos que midiendo la respuesta inmune pueden predecir el riesgo de desarrollar una infección. Por último, revisamos las guías clínicas más recientes y cómo pueden mejorar la atención prestada a estos pacientes.

Palabras clave: Trasplante de órgano sólido; enfermedades infecciosas; inmunosupresión

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INTRODUCTION

Several important advances have been made in the field of solid organ transplant infection in recent years. These advances have given origin to better prophylactic, empirical and directed treatments and a more appropriate and effective follow-up. In this article, we shall review the most significant developments in the field of viral, bacterial and fungal-related infection and the changes they have brought to the daily clinical care. We will also review the latest in immunity assays and their capability in predicting the risk of infection. We also discuss the novelty aspects of recently published guidelines.

WHAT IS NEW IN THE FIELD OF VIRAL INFECTION?

Ganciclovir-resistant (GCV-R) cytomegalovirus (CMV) has emerged as an important opportunistic pathogen after transplantation. Nevertheless, most of the published studies that have focused on this problem had important limitations, such as small number of patients and limited information on clinical outcomes. By designing a retrospective, case-control study which matched 37 genotypically confirmed GCV-R CMV cases to 109 GCV-S CMV controls, Fisher et al. were able to determine the risk factors and outcomes directly associated to GCV-R CMV infection [1]. The authors observed that longer duration of antiviral treatment (153 days [121-208] vs 91 days [41-108], $P < 0.001$) and a higher viral load (61,250 IU/mL [30,000-142,500] vs 8,125 IU/mL [1,913-37,500], $P < 0.001$) were important predisposing factors for developing resistance to GCV. GCV-R CMV infection was also associated to a significantly worse one-year survival rate when compared to GCV-S CMV infection.

Relapse of CMV infection following treatment can occur in 20-30% of transplant recipients. For this reason, following a successful treatment, most clinicians tend to use a long-term secondary prophylactic strategy. Nevertheless, no randomized trials or observational studies have demonstrated the effec-

tiveness of secondary prophylaxis. Gardiner et al. designed a retrospective cohort study, which compared the relapse time of CMV infection between recipients who received secondary prophylaxis and those who did not [2]. All of the 120 patients who received secondary prophylaxis and all of the 50 patients in the control group had been previously treated for an episode of CMV disease. The authors observed that secondary prophylaxis was associated with a reduced risk of early relapse, but that there was limited residual protective effect after stopping prophylaxis. They concluded that secondary prophylaxis could be useful in delaying an early relapse of CMV infection, especially in high-risk patients [2].

Although lung transplant recipients are constantly exposed to respiratory viruses, the epidemiology data of respiratory virus infections in this population and their relationship with chronic lung allograft dysfunction, acute rejection and opportunistic infections are not well known. A recent prospective study, performed from 2009 to 2014, enrolled 98 lung transplant recipients. A total number of 1094 nasopharyngeal swabs were collected from these patients and analyzed by multiplex polymerase chain reaction [3]. These included asymptomatic patients, patients diagnosed with upper or lower respiratory tract infection and patients with biopsy-proven acute rejection. The mean follow-up period was 3.4 years. The authors described that the incidence of respiratory virus infections in lung transplant recipients was very high (a 23.6% positivity rate) and associated with direct effects (tracheobronchitis and pneumonia) and indirect effects (immediate allograft dysfunction, *Pseudomonas aeruginosa* colonization and infection, and CMV replication and disease) [3].

Complications after influenza infection in solid organ transplant recipients can be severe. It is recommended that all recipients receive the annual inactivated trivalent influenza vaccine. Although this strategy is the most effective approach in reducing the burden of influenza disease, it is well known that the rates of seroprotection in this group of patients is generally lower than of the general population. TRANSGRIPE 1-2 is a phase 3, randomized, controlled, multicenter, open-label clinical trial. It hypothesized that the rate of seroprotection could be increased by administering a second dose of the influenza vaccine 5 weeks after the first dose in solid organ transplant recipients [4]. Approximately 500 liver, kidney, heart and lung transplant recipients were randomly assigned (1:1 ratio) to receive one or two doses of influenza vaccine. The authors observed that the rate of seroprotection was higher in the two doses group for all the influenza virus analyzed: 54% vs 43.2% (OR 1.54 [95% CI, 1.05–2.27]; $P = 0.026$) for influenza A(H1N1), 56.9% vs 45.5% (OR 1.58 [95% CI, 1.08–2.31]; $P = 0$ .020) for influenza A(H3N2) and 83.4% vs 71.8% (OR 1.97 [95% CI, 1.23–3.16]; $P = 0.004$) for influenza B [4]. There was no difference in the rate of adverse events between both groups. The authors concluded that the administration of two doses of the influenza vaccine was safe and associated with an improved immunological effectiveness (in all the cases the vaccine was administered after the first month of transplantation) [4].

The THINKER study explored deliberated hepatitis C virus (HCV) transmission from donor to receptor in kidney transplantation in the era of direct acting antivirals. The investigators sought to determine if it was safe to transplant kidney grafts from HCV genotype 1-viremic donors to HCV-negative recipients, who were treated for 12 weeks with elbasvir-grazoprevir as soon as HCV viral load became detectable after transplantation [5]. The entire group of 10 kidney transplant recipients developed a positive HCV viral load on day 3 after transplantation and all of them achieved a sustained virologic response 12 weeks after the end of treatment for HCV, with no deleterious effect on the graft function [5].

WHAT´S NEW IN THE FIELD OF BACTERIAL INFECTION?

Should asymptomatic bacteriuria (AB) be systematically treated in kidney transplant recipients? That is the question that the study group of the University Hospital 12 de Octubre (Madrid, Spain) sought to answer. For that, the group prospectively randomized 112 kidney transplant recipients who had undergone transplantation from January 2011 to December 2013 in two groups: the treatment group, in which the episodes of AB were systematically treated, and the control group, in which no treatment was prescribed [6]. The authors observed that only 3.6% of AB episodes had followed by symptomatic urinary tract infection (UTI) caused by the same microorganism, that one-third of pyelonephritis had no preceding AB episode and that 32.7% of AB episodes had spontaneously cleared without antibiotic treatment. The authors concluded that AB systematic screening and treatment (beyond the second month of transplantation and in patients without ureteral stents or urinary catheters) has no apparent benefit [6].

WHAT´S NEW IN THE FIELD OF FUNGAL INFECTION?

Lung transplant recipients have the highest risk for developing invasive pulmonary aspergilosis (IPA) when compared to other transplant groups, such as liver or kidney transplant recipients. The risk factors, prognosis, prophylaxis and treatment of API in lung transplant recipients are well known and optimized. The incidence of IPA in kidney transplantation is much lower than in lung transplantation but the former is performed much more frequently than the latter worldwide. That is why, in absolute terms, there are much more IPA every year in kidney transplantation than in any other type of solid organ transplantation. Notwithstanding, the current knowledge of the risk factors for developing IPA in the first six months of transplantation and the determinants of mortality was limited to case reports or small case series. López-Medrano et al. developed a multinational retrospective cohort study that included 29 hospitals located in 6 different European countries and 4 different American countries [7,8]. The centers included cases of probable or proven IPA cases diagnosed in kidney transplant recipients from January 1, 2000 to December

31, 2013. To determine the risk factors for developing IPA, a control group (1:1 ratio), consisting of the patients who had undergone transplantation immediately before or after the index cases at each center was created; the control group was matched by institution and date of transplantation and had to have survived at least until the diagnosis of IPA in the corresponding index case. A total number of 112 recipients were enrolled (25% proven IPA and 75% probable IPA). The authors concluded that pretransplant Chronic Obstructive Pulmonary Disease (COPD), impaired graft function (defined by the necessity of hemodialysis after transplantation) and the occurrence of bacteremia were risk factors for developing IPA [7]. The diagnosis of IPA within the first 6 months after transplantation (hazard ratio [HR]: 2.29; $P = 0.027$) and bilateral involvement at diagnosis (HR: 3.00; $P = 0.017$) were independent predictors for 6-week all-cause mortality, whereas the initial use of a voriconazole-based therapy regimen showed a protective effect (HR: 0.34; $P = 0.007$) [8].

WHAT'S THE LATEST IN IMMUNITY ASSAYS?

Transplant recipients have a higher risk of developing infections due the use of lifelong immunosuppressive drugs. Both acute and chronic allograft rejection episodes increase this risk as its treatment is based on a substantial increase of the doses of the administered immunosuppressive drugs. In order to reduce the risk of infection, standard prophylactic treatments for CMV, *Pneumocystis jirovecii* or *Toxoplasma gondii* are prescribed. Nevertheless, in most cases, the capability of the immune system to build a response against these microorganisms is not measured. Mian et al. designed a prospective observational cohort study using a new global cell-mediated immunity (CMI) assay (QuantiFERON Monitor® [QFM®], Qiagen), which measures plasma interferon-gamma (IFN-γ) levels after stimulation of whole blood with a combination of antigens that provokes both the innate and adaptive of the immune system [9]; IFN-γ levels were measured at month 1, 3, and 6 after transplantation [9]. The authors hypothesized that a lower immune response would be associated with an increased risk of infection, while a normal/high response would be protective. Of the 151 consecutive solid organ transplant recipients who were enrolled in the study, 137 had a CMI measurement at least at one point during follow-up. CMI increased during follow-up; the difference of IFN-γ levels between recipients appeared to be related with the dose of the administered immunosuppressive drugs, particularly prednisone (median, 15 mg [IQR, 15-20] vs 5 mg [IQR, 5-8]; $P < 0.0001$) and mycophenolate (median, 720 mg [IQR, 720-720] vs 530 mg [IQR, 360-720]; $P < 0.0001$) [9]. There were no significant differences of the INF-γ levels between patients treated for rejection and those that had not been diagnosed with rejection. Globally, patients who had developed at least one episode of infection during follow-up had significantly lower IFN-γ levels at month 1 ($P = 0.040$), month 3 ($P = 0.050$) and month 6 ($P = 0.006$) [9]. Patients with at least one episode of opportunistic infection also had lower IFN-γ levels in month 3 ($P = 0.024$) and month 6 ($P = 0.014$) after transplantation. The authors concluded that CMI testing could be useful in predicting the risk of infections after transplantation, although further studies would be required to determine the optimal IFN-γ level cutoff [9].

WHAT'S NEW IN RECENT GUIDELINES?

Guidelines are extremely useful for daily clinical care. They help clinicians to optimize their therapy and guide towards the most useful complementary tests depending on the clinical context. Three interesting guidelines have been published recently. Torre-Cisneros J et al. have published an expert consensus document concerning the management of CMV in this type of patients, which includes prophylactic and directed treatment, therapeutic alternatives for ganciclovir-resistant CMV infections and future strategies such as immunological therapy and new drugs [10]. Aguado JM et al. have published several recommendations concerning the management of infections by extended-spectrum β-lactamases (ESBL)-producing Gram-negative bacilli, carbapenemase-producing Enterobacteriaceae, carbapenemase-producing *Pseudomonas aeruginosa* and carbapenemase-producing *Acinectobacter baumannii* in solid organ transplant recipients [11]. Antibiotic alternatives and possible therapeutic schemes are detailed according to microorganism and mechanism of resistance. Finally, Clemente W et al. have published their recommendations on the management of endemic or geographically restricted diseases in solid organ transplant recipients [12]. The supplement, which counted with the expertise of clinicians from 13 different countries representing four continents, includes a carefully written review of relevant diseases such as tuberculosis, Chagas disease, leishmaniasis, malaria, strongyloidiasis, schistosomiasis, travelers' diarrhea, arboviruses (Chikungunya, Dengue, Yellow Fever and Zika), endemic fungal infections (histoplasmosis, paracoccidioidomycosis and sporotrichosis, coccidioidomycosis and *Cryptococcus gattii* infections) and viral hepatitis. The authors have also reviewed the most effective vaccines to mitigate the risk of vaccine-preventable diseases among this immunosuppressed population [12].

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Central nervous system infections in immunocompromised patients

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ABSTRACT

Diagnosis of CNS infections remains a great challenge in immunocompromised patients with solid cancer or hematological disorders, as it happens with transplant recipients, since symptoms might both be masked and be mimicked by other conditions such as metabolic disturbances or consequences of antineoplastic treatment and the administration of immunosuppressive drugs. Thus, awareness of this complication is crucial and any suspicion of a CNS infection should lead to make an early diagnosis and to choose an appropriate empirical treatment to improve the outcome in this population.

Keywords: Central nervous system (CNS) infection, immunocompromised patient, cancer, hematopoietic cell transplantation, solid organ transplantation.

Infecciones del sistema nervioso central en el huésped inmunodeprimido

RESUMEN

El diagnóstico de las infecciones del SNC en pacientes inmunocomprometidos con cáncer sólido o neoplasias hematológicas, junto a los receptores de trasplantes, sigue siendo todo un desafío clínico. Ello es debido a que la semiología podría ser enmascarada y mimetizada por otras condiciones y factores como las alteraciones metabólicas o ser consecuencia del tratamiento antineoplásico o de la administración de fármacos inmunosupresores. Por ello, el conocimiento de esta complicación es crucial y cualquier sospecha de infección del SNC debería conducir a un diagnóstico adecuado en tiempo y forma y a un tratamiento apropiado con el fin de mejorar el pronóstico evolutivo en esta población de enfermos.

Palabras clave: Infecciones del sistema nervioso central, paciente inmunocomprometido, cáncer, trasplante de progenitores hematopoyéticos, trasplante de órgano sólido.

INTRODUCTION

Infections of the central nervous system (CNS) are infrequently diagnosed in immunocompetent patients, but they do occur in a significant proportion of immunosuppressed and cancer patients, such as patients receiving solid organ transplants (SOT) or with hematological disorders including those with hematopoietic stem cell transplantation (HSCT) [1,2,3].

With improved treatments, patients with many types of cancer survive longer. However, both the acute adverse effects of more intensive therapies and the risks of chronic immunosuppression have led to a diverse and evolving spectrum of CNS infections. The presentation and course of CNS infections in cancer and immunosuppressed patients may be different from those in patients without cancer or with immunocompetent status, complicating and delaying an accurate diagnosis. New syndromes related both to the underlying malignancies and to their treatment, including HSCT in hematological cancer, continue to emerge. Noninfectious disorders such as adverse drug effects, vascular lesions, and radiation effects can mimic CNS infections [4]. The major deficits predisposing patients with cancer to CNS infection are neutropenia, barrier disruption, B-lymphocyte or immunoglobulin deficiency, and impaired T lymphocyte-mediated immunity. Evolving patterns of drug resistance and prophylactic antimicrobial regimens have altered the timing and range of organisms causing infections. Increasingly intensive immunosuppression has made new groups of patients vulnerable to very different and peculiar infections such as progressive multifocal leukoencephalopathy (PML) or limbic encephalitis (LE). New magnetic resonance

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imaging (MRI) sequences offer the potential to diagnose such infections earlier, at a stage when they are more treatable.

Despite improved prophylactic and therapeutic antibiotic regimens, CNS infections remain an important source of morbidity and mortality among several cancer patient groups, particularly those patients undergoing craniotomy and those with hematologic malignancies receiving either HSCT or other intensive chemotherapy regimens. The diagnosis and management of CNS infections in cancer or immunosuppressed patients raises a formidable challenge to neurological consultants. Timely, effective care for these patients requires attention to underlying patient disease and treatment regimen risk factors, prophylactic and vaccination strategies, transfusion safety issues, community and nosocomial epidemiologic trends, travel and zoonotic exposure histories, and changing microbial susceptibilities. Additionally, it is important to recognize that (a) clinical presentations of infections in immunocompromised patients may be atypical or may mimic noninfectious processes, (b) two or more disparate diseases may coexist, and (c) patients can be at risk for infection not only during cancer treatment or transplant procedure, but also before and for an extended period after therapy or transplantation [5].

CNS INFECTIONS IN PATIENTS WITH HEMATOLOGICAL DISORDERS (INCLUDING AUTO- AND ALLOGENEIC STEM-CELL TRANSPLANTATION)

By far, CNS infections are much more frequent and serious in patients with allo-HSCT than in patients with auto-transplant. Patients undergoing allo-HSCT are among those with the highest risk for CNS infections with an overall incidence of up to 15% [6]. Fungi (*Aspergillus* spp.) and *Toxoplasma gondii* are the predominant causative agents. Mucormycosis is diagnosed in ~0.1% of all patients with hematological disorders, but an increased incidence (1.0%-1.9%) has been reported among patients with acute myeloid leukemia (AML). The lungs are frequently infected in mucormycosis, but CNS might be involved in 10%–20% of patients. Among virus, PML is a rare (<1%), but frequently fatal CNS disease caused by the JC virus. It mainly affects allo-HSCT recipients, but also patients after rituximab-based treatment strategies or with multiple lines of immunosuppression. Bacterial CNS infections are rarely diagnosed in patients with hematological disorders, and they occur more frequently in patients with intraventricular devices or after neurosurgical interventions. The diagnosis of CNS infections is based on neuroimaging, cerebrospinal fluid examination and biopsy of suspicious lesions in selected patients. However, identification of CNS infections in immunocompromised patients could represent a major challenge since metabolic disturbances, side-effects of antineoplastic or immunosuppressive drugs and CNS involvement of the underlying hematological disorder may mimic symptoms of a CNS infection [7]. As in the context of SOT recipients, neurologically important syndromes and problematic presentations (table 1) include posterior reversible encephalopathy syndrome (PRES), post-transplantation lymphoproliferative disorder (PTLD) [8] and immune reconstitution inflammatory syndrome (IRIS). The prognosis of CNS infections is generally poor in these patients, despite the introduction of novel substances (e.g. voriconazole, posaconazole, isavuconazole) has improved the outcome in distinct patient subgroups.

CNS infections are a significant clinical problem after HSCT related to poor survival. They were more frequent after umbilical cord blood transplantation (UCBT) compared to HLA-matched sibling donor stem cell transplantation (MST). The incidence, clinical characteristics, prognostic factors, and outcome of CNS infections in consecutive patients receiving UCBT or MST were recently analyzed by a Spanish scientific group [9]. Thirty-four CNS infections were documented at a median time of 116 days after transplantation (range, 7 to 1161). The cumulative incidence (CI) risk of developing a CNS infection was 0.6% at day +30, 2.3% at day +90, and 4.9% at 5 years. The 5-year CI of CNS infection was 8.2% after UCBT and 1.7% after MST ($P < .001$). The causative micro-organisms of CNS infections were fungi (35%), virus (32%), *Toxoplasma* spp. (12%), and bacteria (12%). Fungal infections occurred in 11 patients after UCBT and 1 after MST and were caused predominantly by *Aspergillus* spp. (in 8 cases), followed by *Cryptococcus neoformans* (2 cases), *Scedosporium prolificans* and *Mucor* (one case each). Except for 1 patient, all died from CNS fungal infection. Viral infections occurred in 9 patients after UCBT and 1 after MST and were due to human herpes virus 6, cytomegalovirus, and varicella zoster virus. CNS toxoplasmosis was diagnosed in 3 patients after UCBT and 1 after MST. Other pathogens were *Staphylococcus* spp, *Nocardia* spp, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. Twenty of the 34 patients (59%) died from the CNS infection. UCBT and disease stage beyond first complete remission were independently associated with the risk of developing CNS infections. The 5-year overall survival was 19% in patients who developed a CNS infection and 39% for those who did not.

Some principal aspects regarding the management of CNS infections in patients with hematological disorders should be considered:

(a) The management of CNS infections in patients with hematological disorders requires a high level of awareness, as neurological symptoms could be nonspecific and caused by noninfectious conditions related to the underlying disease and/or side-effects of antineoplastic or immunosuppressive treatment. An additional differential diagnostic consideration to explain a neurological syndrome in a cancer patient with known or suspected CNS infection is a complication of antibiotic therapy itself, as summarized in table 2.

(b) While clinical presentations of CNS infections in immunocompetent hosts are broadly categorized into meningitis, meningoencephalitis, encephalitis, cerebritis/abscess formation and infection of intracerebral devices, diminished inflammatory responses in immunocompromised patients can lead to only subtle symptoms. Mass lesions can be blurred by rather nonspecific cerebral dysfunctions such as confusion or altered consciousness.

Table 1 Differential diagnosis of CNS infection by predominant clinical and MRI Syndrom.

Leukoencephalopathy	Stroke (s)	Limbic encephalitis	Mass lesion (s)	Brainstem
INFECTIONS				
PML-JCV	VZV, CMV*	Herpes simplex types 1 & 2	*Aspergillus* and other molds	*Listeria monocytogenes*
	Emboli (due to endocarditis)	HHV-6	Bacteria (*S. aureus, Nocardia, Bacteroides*)	*Cryptococcus neoformans*
	Vasculitis post-meningitis		*Toxoplasma gondii*	VZV
	Aspergillus, Mucor spp.		EBV associated CNS lymphoma	PML-JCV
NON-INFECTIOUS CONDITIONS				
IRIS, PRES, ADEM	Radiation-related arteriopathy	Hashimoto encephalopathy	IRIS	Wernicke encephalopathy
Pontine / extrapontine osmotic demyelination	Non-bacterial thrombotic endocarditis	Paraneoplastic syndromes (anti-HU, Ma, NMDAR, VGKC)	Secondary tumor (lymphoma, meningioma, astrocytoma, metastases)	Osmotic demyelination
Amphotericin B	CNS vasculitis	Repetitive seizures	Radiation necrosis (pseudoprogression)	PRESS
Valproate				GVHD
Rituximab				Radiation necrosis
Radiation injury				

CNS: Central nervous system; PML-JCV: progressive multifocal leucoencephalopathy (due to JC virus); VZV: varicella-zoster virus; CMV: Cytomegalovirus; HHV-6: Human herpes virus 6; EBV: Epstein-Barr Virus; IRIS: inflammatory reconstitution immune syndrome; PRES: Posterior reversible encephalopathy syndrome; ADEM: Acute disseminated encephalomyelitis. MRI gadolinium enhancement variable for all conditions. *CMV: Variable manifestations (encephalitis, myelitis, polyradiculitis).

Table 2 Neurologic toxicities of antimicrobial agents.

Neurologic Problem	Potential causative agents
Seizures	Penicillin G, imipenem/meropenem, aztreonam, gentamicin, ciprofloxacin, cefepime, ceftazidime, metronidazole, amphotericin B, acyclovir (iv), foscarnet, praziquantel
Potentiation of neuromuscular junction transmission blockade	Aminoglycosides, cephalosporins
Pseudotumor cerebri	Minocycline, tetracycline
Ototoxicity/vestibular	Vancomycin, aminoglycosides, erythromycin, tacrolimus
Delirium	Cefepime, ceftazidime, ciprofloxacin, metronidazole, foscarnet, praziquantel, amphotericin B
Visual hallucinations	Voriconazole
Extrapiramidal signs	Amphotericin B
Headache	Ciprofloxacin, fluconazole, itraconazole, foscarnet, praziquantel, trimethoprim/sulfamethoxazole
Dizziness /cerebellar signs	Metronidazole, aminoglycosides, minocycline, isoniazid, fluconazole, itraconazole, varicella vaccine (ataxia)
Posterior reversible encephalopathy syndrome	Linezolid, roxithromycin
Lymphocytic meningitis	Trimethoprim/sulfamethoxazole, cephalosporins, iv. immunoglobulin, valacyclovir
Tremor	Acyclovir, cephalosporins
Optic neuropathy	Ethambutol, linezolid
Serotonin syndrome	Linezolid (with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors)

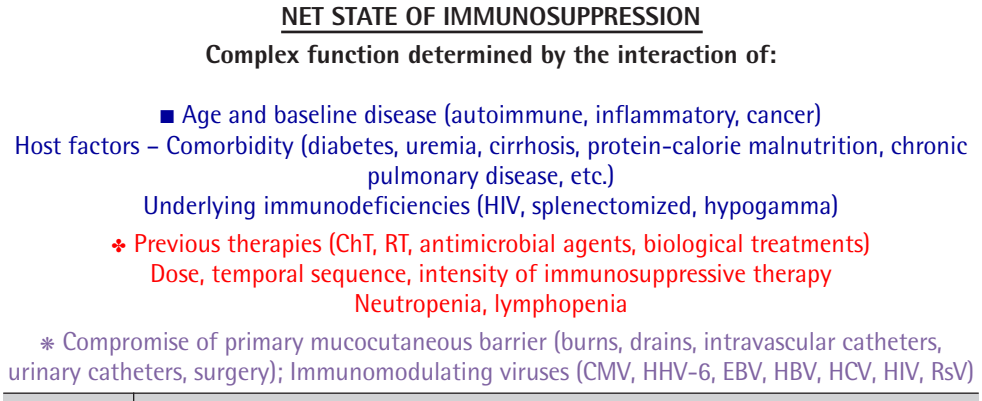

Figure 1 | **Net state of immunosuppression: determining concept of risk of infection.**

ChT: Chemotherapy; RT: Radiotherapy; RsV: Respiratory virus.

(c) Defined patient groups predispose for infections with certain pathogens based on their pattern of immunosuppression (defects in cell-mediated immunity versus defective humoral immunity). Bacterial, fungal and viral CNS infections typically occur in neutropenic patients. Defects in T-cell immunity or in function of macrophages predispose for cerebral toxoplasmosis and cryptococcal meningitis.

(d) Variations in the frequency of causative organisms (e.g. *Toxoplasma* spp. *Histoplasma capsulatum*, *Mycobacterium tuberculosis*) due to regional endemic differences should be taken into account.

Regarding diagnosis, any suspicion of CNS infection should immediately trigger adequate diagnostic procedures including neuroimaging, cerebrospinal fluid (CSF) examination and, in selected cases, biopsy of focal lesions. CSF analyses including various methods such as staining and microscopy, culturing, serological techniques and PCR assays (nowadays with multiplex PCR techniques) are crucial diagnosing meningoencephalitis which is typically caused by viruses, *Candida* spp., bacteria or more rarely by *Cryptococcus* spp. For these CNS infections, brain biopsy is required only in selected cases. Focal lesions, typically caused by *Toxoplasma* or *Aspergillus* spp. are commonly diagnosed by histopathology of suspicious lesions. Histopathological work-up should be done using adequate staining methods such as Calcofluor white. Routine parameters in the CSF are frequently nonspecifically altered in these patients. Neuroimaging should commonly be based on MRI since it is more sensitive than computed tomography (CT) scan for diagnosis of the majority of CNS infections. Further diagnostic methods such as positron emission tomography (PET) might help in selected patients to differentiate infectious from noninfectious CNS lesions.

Given the dismal outcome of delayed treatment in patients with hematological disorders and CNS infection, antimicrobial treatment should be initiated promptly once collection of CSF and blood cultures have been completed. After isolation and in vitro susceptibility testing of a (potentially) causative pathogen, antimicrobial treatment should be modified accordingly. Recommendations for empiric, pre-emptive and targeted treatment are specified and available in several guidelines, articles and consensus documents [10], providing supplementary material to our manuscript. Due to the lack of systematic data, decisions about the duration of antimicrobial treatment should be assessed individually. Treatment strategy (such as antimicrobial drug therapy with or without surgery), resolution of symptoms and recovery of the individual immune-status, as defined by the presence of neutropenia, hypogammaglobulinemia and graft versus-host disease should therefore be taken in account. In patients with persisting complex immunodeficiencies, targeted antimicrobial treatment might be followed by maintenance treatment (e.g. for cerebral toxoplasmosis, cytomegalovirus encephalitis or cryptococcal meningitis). To improve efficacy and minimize toxicity, therapeutic drug monitoring (TDM) might be useful for antimicrobial agents, such as 5-fluorocytosine (5-FC), voriconazole and posaconazole. TDM might be of particular relevance in patients with hematological disorders since impaired gastrointestinal resorption and interferences with concomitant medication are common in this population. Adjunctive treatment may include neurosurgery, platelet transfusion and administration of corticosteroids, anticonvulsants, sedatives or antipyretics.

NEUROLOGICAL COMPLICATIONS DUE TO INFECTION IN SOLID ORGAN TRANSPLANTATION (SOT)

The prevention, diagnosis, and management of infectious disease (including CNS infections) in transplantation are major contributors to improved outcomes in organ transplantation. The risk of serious CNS infections in organ recipients is determined by interactions between the patient's epidemiological exposures and net state of immunosuppression. In organ recipients, there is a significant incidence of drug toxicity and a propensity for drug interactions with immunosuppressive agents used to maintain graft function. Thus, every effort must

be made to establish specific microbiologic diagnoses to optimize therapy. A timeline can be created to develop a differential diagnosis of infection in transplantation based on common patterns of infectious exposures, immunosuppressive management, and antimicrobial prophylaxis. Application of quantitative molecular microbial assays and advanced antimicrobial therapies have improved care. Pathogen-specific immunity, genetic polymorphisms in immune responses, and dynamic interactions between the microbiome and the risk of infection are beginning to be explored.

Approximately one-third (between 10% and 85% according to different series) of SOT patients will experience a neurological complication [11]. While the spectrum of neurological complications varies with the type of organ transplanted, the indication for the procedure, and the intensity of long-term required immunosuppression, major neurological complications occur with all SOT types. Neurological complications common to all SOT not caused by transplanted organ failure are frequently attributable to immunosuppressive regimens. Common neurological complications are seizures, CNS infections, encephalopathy, and stroke. Few neurological complications occur exclusively in a specific transplant population, but both in the early days and throughout their post-transplantation course, recipients of different tissues and organs have predictably varied complication patterns. Among SOT recipients, liver transplant recipients, particularly those with fulminant hepatic failure and coagulopathy, have the most serious medical problems at the time of their transplant with concomitantly more early complications. Months to years after SOT, complication profiles reflect the degree and duration of immunosuppression necessary to prevent rejection. Thus, heart and intestinal/pancreas recipients, the most heavily chronically immunosuppressed groups, are the most prone to late infectious complications.

Those who develop CNS abnormalities will have clinical presentations ranging from generalized encephalopathy or headache to focal neurological deficits. The etiology of these abnormalities is often obscure; symptoms are altered by immunosuppressive therapy. There is an urgency to establish a specific etiological diagnosis to guide therapy. The major categories of "CNS processes" include infection, drug toxicity, anatomic processes (stroke, cancer, vasculitis), and metabolic derangements including those associated with graft dysfunction. These etiologies, infections and non-infectious causes of CNS abnormalities, often coexist in the transplant recipient [12]. For example, post-transplant graft dysfunction (uremia, cardiac, or hepatic insufficiency; hypoxia) can be complicated by infection (sepsis, wound infection, nosocomial pneumonia), drug toxicity (CNS effects of calcineurin inhibitors), stroke, or bleeding. The initial evaluation must identify potentially life-threatening processes. The risk for CNS infection after transplantation rests on two fundamental determinants: Prior exposures and the net state of immunosuppression. The epidemiological exposures of a transplant recipient include those from the hospital environment, from community exposures, from the host as reactivation of latent infections, and from the organ donor. The "net state of immunosuppression" is a concept encompassing patient-specific factors that determine vulnerability to infection (figure 1).

With respect to the timeline of CNS processes, multiple factors contribute to altered mental status and neurological disorders in the post-transplant setting. The intersection of epidemiology and the net state of immunosuppression characterizes the evolving risk for CNS infections. Variability exists with immunosuppressive regimens, antimicrobial prophylaxis, and epidemiology. On these alterations the neurological effects caused by metabolic alterations and drug toxicities are superimposed. This approach creates a timeline for common and more obscure post-transplant CNS syndromes, distributed in a group of successive periods or consecutive phases, which include: Postoperative phase (1–4 weeks), early post-transplant syndromes (1–6 months) and late post-transplant syndromes (6 months and beyond).

CNS infection in the transplant recipient is a medical emergency. A specific diagnosis of CNS processes in transplant recipients is essential for management. The spectrum of causative organisms is broad. Classic signs (headache, meningismus, fever, Kernig and Brudzinski signs, or papilledema) are often absent. Subtle cranial nerve abnormalities may be useful in diagnosis. Neurological signs of infection may be obscured by hepatic encephalopathy, uremia, hypoxemia, drug effects (calcineurin inhibitors, fluoroquinolones, trimethoprim-sulfamethoxazole), systemic infection, or alcohol withdrawal and depression. Empirical therapy has risk for drug toxicities and interactions. Reduced immunosuppression may provoke or exacerbate graft rejection. Immunosuppressed patients with focal neurological deficits require urgent brain imaging. Most transplant recipients with altered mental status also require imaging. CT or MRI studies without contrast (to preserve renal function) may demonstrate mass lesions but lack sensitivity for white matter changes.

Many CNS infections spread from the lungs or sinuses. Thus, "metastatic" evaluations are needed, notably for infections due to fungi (*Aspergillus*, agents of mucormycosis, *Scedosporium* or *Cryptococcus*) [13], bacteria (*Nocardia* spp.) or parasitic diseases (*Strongyloides stercoralis*). Important viral infections include herpes simplex virus meningoencephalitis, cytomegalovirus, JC virus (PML), West Nile virus, and varicella zoster virus. Common bacterial infections include *Listeria monocytogenes*, mycobacteria, *Nocardia* and occasionally *Salmonella* species. Parasites include protozoa and helminths such as *Toxoplasma gondii*, *Microsporidia*, and *Strongyloides*. Specific diagnosis is essential. Empirical therapy must "cover" *Listeria* (ampicillin), *Cryptococcus* (Amphotericin B and/or fluconazole), and herpes simplex virus (acyclovir or ganciclovir), common bacterial pathogens (vancomycin/linezolid, ceftriaxone), and known colonizing organisms while awaiting data from lumbar puncture, blood cultures, and radiographic studies. Included in the differential diagnosis are non-infectious etiologies including calcineurin inhibitor toxicity, PRES, PML, lymphoma (PTLD), and other malignancies. Unique epidemiologic exposures (e.g. Chagas disease, Lyme) must be considered.

Bactericidal or fungicidal agents with CNS penetration are preferred. Broad-spectrum coverage should be maintained until a diagnosis is achieved. The management of immunosuppression must be individualized, such as reducing T-cell suppression in viral infections including EBV-associated PTLD or JC virus–induced PML. Reduced immunosuppression risks immunological rebound with graft rejection, increased inflammation and edema, and/or IRIS manifesting as worsening of CNS symptoms in the face of appropriate therapy and without disease progression. IRIS has been documented in transplant recipients with CMV, tuberculosis, and cryptococcal disease. Acute reductions in corticosteroids during CNS infection, in particular, may provoke hydrocephalus in cryptococcal meningitis or infectious vasculitis or encephalitis flare-ups. CNS PTLD may not respond to reduced immunosuppression; irradiation is often beneficial and CD20+ tumors may respond to monoclonal antibody therapy, although the penetration and activity of rituximab in CNS is insufficient. Immunosuppression must be reinstated when appropriate to avoid graft rejection. Increases in immunosuppression may be helpful, particularly for specific pathogens such as *Streptococcus pneumoniae*. Increased adrenocorticoids may reverse persistent hypotension due to adrenal insufficiency from infection or chronic glucocorticoid use. Some transplant recipients require procedural interventions for management of CNS infection. Cryptococcal meningitis may cause elevated intracranial pressure with hydrocephalus requiring serial lumbar punctures or ventricular shunting. Neurosurgical intervention may be required for acute hydrocephalus due to intraventricular development or rupture of abscesses blocking CSF ventricular flow. Surgical debridement of bacterial abscesses or fungal lesions (e.g., mucorales) may be required for diagnosis and to gain control of progressive, invasive infection [14].

CONCLUSIONS

The diagnosis and management of CNS infections in immunocompromised patients remains challenging and requires constant attention to emerging infections, prophylactic strategies, transfusion safety issues, epidemiologic trends, travel histories, changing microbial susceptibilities, synergistic infections, and evolving cancer regimens or anti-rejection drugs that will continue to impact the nervous system. Finally, the effective consultant should never discount the possibility that two or more disparate diseases (neoplastic, infectious and autoimmune) may exist concurrently. Despite efforts to stratify patients by risk factors, clinical syndromes, and appropriate diagnostic studies, diagnostic and therapeutic dilemmas are common and outcomes remain, despite the *neuroinfectologist's* best efforts, frequently disappointing.

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Top-ten papers in Infection Control (2015-2017)

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ABSTRACT

Healthcare-associated infections are a main Public Health challenge. In the era of antimicrobial resistance, more effective Infection Control Programs are needed. In this review we will discuss some publications related to hand hygiene (should the patients participate in the improvement programs?); some new strategies to enhance terminal room disinfection and important controversies on contact precautions policies (should we abandon them?). In the last year, there have been as well some reports that provide new insights in *Clostridium difficile* infection and in the impact of educational antimicrobial stewardship programs.

Key words: infection control,, cross infections, antimicrobial stewardship.

Mejores publicaciones sobre control de infección

RESUMEN

Las infecciones relacionadas con la asistencia sanitaria constituyen un gran desafío de salud pública. En la era de la resistencia a los antimicrobianos se necesitan programas de control de la infección más eficaces. En esta revisión, analizaremos algunas publicaciones relacionadas con la higiene de las manos (¿deberían los pacientes participar en los programas de mejora?); algunas nuevas estrategias para mejorar la desinfección terminal y controversias importantes sobre las políticas de precauciones de contacto (¿deberíamos abandonarlas?). En el último año, también ha habido algunas publicaciones relevantes que proporcionan nuevos conocimientos sobre la epidemiología de la infección por *Clostridium difficile* y sobre el impacto de las intervenciones educativas enmarcadas en los PROA.

Palabras clave: control de la infección, infecciones cruzadas, administración de antimicrobianos

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HAND HYGIENE

Hand hygiene (HH) is the core element of infection prevention and control. In 2016, Stewardson et al. [1] published a study aimed to assess the effect of enhanced performance feedback and patient participation on HH compliance in the setting of a multimodal promotion. They did a single-centre, cluster randomised controlled trial (Geneve, Switzerland). After a 15-month baseline period, they randomised 67 hospitalization wards to one of three groups: control, enhanced performance feedback or enhanced performance plus patient participation. They made 1367 observations and evaluated 12579 opportunities of HH. Remarkably, basal compliance rates were around 60% in the three study arms. They found an overall increase in HH compliance of HCW from 65 to 74%. This increase between the baseline and intervention periods was significantly larger in wards exposed to both enhanced performance groups. However the improvement attributable to the patient participation did not reach statistical significance. This study highlights the challenges with randomised trials aimed to assess behaviour change. Authors recognize that there was a cross-contamination effect which could not be avoided.

The optimal HH technique remains poor defined. Pires et al. [2] performed a laboratory-based experimental study to evaluate the effect of hand-rubbing duration on the antimicrobial efficacy of HH. They demonstrated that performing hand rubbing for 15 seconds was not inferior to 30. Lack of time had been identified as one of the major factors which negatively influenced on HH compliance. Therefore reducing the time needed to perform an optimal HH gesture

could lead to augmented HH compliance. Nevertheless, this study has been performed in a laboratory experimental setting which could influence in the applicability of results to real clinical practice.

ENVIRONMENT & UNUSUAL OUTBREAKS

Environmental control and adequate disinfection could be involved in multidrug-resistant microorganisms cross-transmission and development of unusual outbreaks. We have selected four papers related to this aspect of infection control: one clinical trial report regarding the importance of room disinfection and three reports of unusual outbreaks due to environmental contamination.

Anderson et al. [3] published in 2017 the results of a pragmatic, cluster-randomized, crossover trial conducted at nine hospitals in the southern USA. They tried to assess the effects of four different strategies for terminal room disinfection on acquisition of multidrug-resistant microorganisms or *Clostridium difficile* strains. Rooms from which a patient with infection or colonisation with a target microorganism was discharged were terminally disinfected with one of four strategies: reference (quaternary ammonium disinfectant except for *C. difficile*, for which bleach was used); UV (quaternary ammonium disinfectant and disinfecting ultraviolet [UV-C] light except for *C. difficile*, for which bleach and UV-C were used); bleach; and bleach and UV-C. The next patient admitted to the targeted room was considered exposed. More than 31,200 patients were exposed; 21,395 met all inclusion criteria so more than 5,000 patients were included in every group. They found that patients admitted to rooms previously occupied by patients harbouring a multidrug-resistant microorganism or *C. difficile* were 10-30% less likely to acquire the same organism if the room was terminally disinfected using an enhanced strategy. The largest risk reduction occurred when a UV-C device was added to the standard disinfectant strategy. However, no significant decrease in outcomes was observed when they used bleach or bleach and UV. Hence, the incidence of *C. difficile* infection among exposed patients was not changed after adding UV to cleaning with bleach. This is the second clinical trial which has investigated the importance of an enhanced disinfection strategy in acquisition of multidrug-resistant microorganisms and the first one in using a UV device. Remarkably, authors assessed hand hygiene compliance, room cleaning compliance and colonisation pressure, which can play a role in the transmission risk. However, the study has some limitations: first, active surveillance cultures and molecular analysis to confirm crossed transmission were not conducted. Finally basal compliance rates for standard procedures were higher than usual which can impact on the applicability of results in other settings.

In 2016 Cheng et al. [4] reported a hospital outbreak of pulmonary and cutaneous zygomicosis occurred over a period of 2 months in Hong Kong (China). Six immunosuppressed patients developed pulmonary and/or cutaneous infection by *Rhizopus microsporus* through direct inhalation and skin contact of contaminated linen items supplied by a designated laundry for the Hospital. The fungal isolates from clinical and environmental samples were identified by morphology and gene sequencing. They sampled linen items supplied by both the designated laundry and by 9 other laundries in Hong Kong, as controls. 27% of the clothing from the designated laundry was positive for zygomicetes versus none of the linen items collected from the control laundries. 61% environmental samples and 100% air filters samples taken at the designated laundry were positive for zygomicetes. Three patients (50%) died.

This is the first major outbreak of pulmonary and cutaneous zygomicosis in immunosuppressed patients due to linen items. Until now, only 12 hospital outbreaks have been related to laundered linen items, and there is no public health consensus on the standard of hygienically clean linen items.

A study conducted by Potron et al. [5] between 2012 and 2014 described the first outbreak of OXA-204-producing Enterobacteriaceae in Europe. They investigated a total of 29 OXA-204 β-lactamase-producing Enterobacteriaceae isolates. Of these 29 OXA-204 producers, 27 were isolated from 22 patients located in the same geographical area (Paris, France). These results led the investigators to do an epidemiological investigation. An endoscope was identified as the possible source of the outbreak: 17 patients had had direct contact with the endoscope while five were considered as secondary cases through patient-to-patient transmission on a clinical ward. Additionally, retrospective screening of all patients who had endoscopy with the suspected contaminated endoscope identified two colonised patients who underwent endoscopy as outpatients. Finally 14 patients were infected (four biliary infections, one hepatic abscess and nine urinary tract infections) and 12 patients were colonised. Endoscopy-associated transmission of carbapenemase-producing Enterobacteriaceae (CPE) might result in long-term carriage of the acquired CPE.

Finally, in 2017 van Ingen et al. [6] conducted a molecular epidemiological investigation by applying whole-genome sequencing on clinical and environmental *Mycobacterium chimaera* isolates after cardiac surgery from four European countries. They included 24 *M. chimaera* isolates from 21 cardiac surgery-related patients in Switzerland, Germany, the Netherlands and UK and 218 *M. chimaera* isolates from various types of heater-cooler units -HCUs- (that are used to control temperature within the extracorporeal circulation during cardiac surgery) from LivaNova and Maquet brand HCU production sites and unrelated environmental sources and patients. In summary, an extensive molecular epidemiological investigation including a large series of affected patients, the two market-leading brands of HCUs and their production sites suggests the possibility that the majority of cases of cardiothoracic surgery-related severe *M. chimera* infections diagnosed in different countries resulted from a single common source of infection, LivaNova HCUs that were contaminated during production in Germany.

CONTACT PRECAUTIONS AND DURATION OF COLONISATION IN LONG TERM ACUTE CARE HOSPITALS

In the last years, many studies analysing the impact of discontinuing contact precautions (CPs) for different multidrug-resistant microorganisms in the acute care setting have been published. We have selected a systematic literature review and meta-analysis through December 2016 [7]. Fourteen studies met inclusion criteria and were included in the final review. Six studies discontinued CPs for methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) simultaneously, 3 for MRSA and 2 for VRE exclusively, 2 for extended-spectrum β-lactamase-producing *Escherichia coli* and 1 for *Clostridium difficile* infection. Most of the studies (10 studies) were conducted in the United States. Authors reported that discontinuing CPs for endemic MRSA and VRE has not resulted in a detectable increase in MRSA or VRE infection rates. This lack of effectiveness at preventing endemic MRSA and VRE infections could be due to low HCW compliance with CPs or low transmission of endemic infections. In addition, unintended consequences associated with CPs have been well documented. The importance of this meta-analysis recalls on the rethink exercise of recommendations which were suggested in 1970 when there was minimal surveillance for health-care associated infections and hand washing was the standard of care. Nowadays, many U.S hospitals are focusing resources on horizontal infection control strategies to prevent multidrug-resistant organisms. The current meta-analysis has important limitations: the inclusion of many studies that were before-after quasi-experimental studies is subjected to multiple biases and the follow-up time of the studies included was short (only one study had a long follow-up, 10 years).

A quality improvement program in long-term acute care hospitals (LTACHs) has been recently reported by Haverkate et al. in 2016 [8]. They determined the duration of colonisation with carbapenemase-producing *Klebsiella pneumoniae* (KPC) during admission and between discharge and re-admission in a cohort of patients from 4 LTACHs in Chicago. During the study period, a bundled intervention was implemented. This infection control bundle involved daily bathing of all LTACH patients with 2% chlorhexidine gluconate (CHG) education of the medical staff on KPC and infection prevention, adherence monitoring (focusing on hand hygiene), patient and staff cohorting, and surveillance screening. Surveillance screening for KPC comprised rectal swab culture screening on admission and every other week for all LTACH patients. During a median 1-month LTACH stay, 83% of patients are still colonised with KPC after a 4-weeks period. Even more, 50% of patients who are readmitted after 9 months are still colonised. According to this, patients who are found to be KPC carriers remain colonised throughout their hospitalization and it seems justified to isolate KPC-positive patients for the duration of their hospital stay. Taking account the limitations of the study, they didn't perform molecular studies, so there is no way to know if a patient carried the same strain of KPC or if it was a recolonisation.

NEW INSIGHTS IN *CLOSTRIDIUM DIFFICILE* EPIDEMIOLOGY

Clostridium difficile infection (CDI) is the most common cause of diarrhoea in hospital. CDI occurs when there is a susceptible host and sufficient exposure to the organism. Many factors may increase host susceptibility to CDI, but the most crucial host-related risk factor is exposure to antibiotics. We have selected a recent project conducted by Freedberg et al. [9], published in 2016, which remarks the colonisation pressure importance. The aim of the study was to assess whether receipt of antibiotics by prior bed occupant was associated with increased risk for CDI in subsequent patients who occupied the same bed. This was a retrospective study in four affiliated but geographically distinct hospitals in New York City metropolitan area; 100,615 pairs of patients were analyzed. Receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients even after adjusting for potential confounders. The median time from bed admission to CDI when a subsequent patient developed the infection was 6.4 days (IQR 4.0-9.5). The results of this study support the previous findings regarding colonisation pressure (number of patients nearby who already have the infection) by demonstrating that the CDI risk profile of the prior bed occupant is likely to be a part of this *C. difficile* colonisation pressure. The weaknesses of this study fall on the biases of an observational study and biases of selected housing. There are also other limitations: it has been conducted in a single centre, which makes the results non generalizable to other institutions and in a non-outbreak setting, so the relationship between antibiotics and CDI may differ during an outbreak.

ANTIMICROBIAL STEWARDSHIP PROGRAMS

The global increase in antimicrobial resistance has brought along the implementation of intervention programs to promote the appropriate use of antimicrobials. In 2017, Molina et al. [10] published the impact of an educational antimicrobial stewardship program on antibiotic consumption, incidence density of hospital-acquired *Candida* spp. and multidrug-resistant (MDR) bloodstream infections (BSI) and crude mortality rate per 1,000 occupied bed days (OBDs). They conducted a quasi-experimental intervention study over a 5-year period. A multidisciplinary team conducted a multifaceted educational intervention in a tertiary-care hospital. The main activity consisted in peer-to-peer educational interviews between counsellors and prescribers from all departments to reinforce the principles of the proper use of antibiotics without performing any antibiotic changes. A total of 3,176 educational interventions (EIs) were performed with prescribers from all clinical units; more than 1,200 EIs were held in the first year, followed by an average of 500 EIs per year. The average time required for each

interview was 10 minutes. The median consumption dropped from 1,008 (interquartile range [IQR], 980-1,078) to 774 (750-787) DDDs per 1,000 OBDs from the first to the last year. The incidence density of hospital-acquired candidemia and MDR BSI diminished parallel to the antibiotic pressure. Conversely, the incidence density of hospital-acquired BSIs produced by non-MDR strains of the same microorganisms under study did not change during the intervention. All-cause 14-day crude death rate for hospital-acquired candidemia and MDR BSIs was reduced parallel to its incidence. This study proves that an educational intervention can improve antibiotic consumption, infection incidence by MDR and *Candida* spp. and mortality.

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Evaluation questionnaire

VIII Updating Course of Antimicrobials and Infectious Diseases 2018

1. The *mcr*-1 gene is responsible of transferable resistance to:

a) Linezolid
b) Colistin
c) Fluoroquinolones
d) Methicillin

2. Regarding the new cephalosporin "cefiderocol" it is true that:

a) It is active against Enterobacteria but not against *Pseudomonas aeruginosa*
b) It has activity against Enterobacteria and against MRSA
c) It is active against Enterobacteria producing Carbapenemase class A (KPC), B (NDM) and D (OXA-48)
d) It is active against Carbapenemase producing Enterobacteria class A and D, but not class B

3. Regarding the rapid diagnosis technique called LAMP (Loop-Mediated Isothermal Amplification), it is true that:

a) Allows direct detection in clinical samples of different microorganisms in one hour
b) It does not serve to detect carbapenemases from clinical samples, only from cultures
c) It allows to detect the presence of bacteria but not of parasites in clinical samples
d) It is a quick but expensive technique and complicated management in the laboratory

4. Point out the true one regarding gram-positive infections

a) Fuchsic acid achieved equal microbiological eradication as linezolid in IPPB but did not reduce the size of the lesion by 20% in the first 48 hours
b) Ceftaroline showed higher microbiological activity than ceftriaxone against respiratory pathogens, including penicillin-resistant *Streptococcus pneumoniae*, however it is not clinically active in infections in obese or bacteraemic
c) Dalbavancin was shown to be as eradicating as vancomycin in persistent infection models
d) Daptomycin at 10 mg / kg was also active in bacteremia caused by strains of *Enterococcus faecium* regardless of their MIC (< or > 2 mg/l)

5. Point out the false with regard to Gram-negative infections

a) Plazomycin exhibits superior in vitro activity than amikacin and gentamicin against carbapenem-resistant *Enterobacteriaceae,* has less renal toxicity, more healing and more microbiological eradication than colistin in phase III studies in pneumonia, bacteremia and UTI.
b) The in vitro activity of aminoglycosides can be affected by inoculum, by pH and by anaerobiosis. This is important because of its clinical impact.
c) Cefiderocol, the new cephalosporin with siderophore was active against multiresistant *Pseudomonas* spp but not against other non-fermenting bacilli such as *Acinetobacter* spp, or *Stenotrophomonas* spp
d) Ceftazidime-Avibactam was particularly active against class A beta-lactamases (in vivo and in vitro), Aztreonam-avibactam versus class B (enterobacteria and *Pseudomonas* spp) and ceftolozane-tazobactam versus class C (especially *Pseudomonas* spp).

6. Point out the incorrect one in relation to the new antimicrobials

a) LYS228 is a monobactamic in development with binding to PBP3 and extraordinary activity against MBL while also maintaining activity against the other beta-lactamases (OXA, KPC, CTXm, etc.)
b) New aryloxazolidinones bound to topoisomerase activity are being developed against all ESKAPE pathogens
c) Meropenem-vaborbactam is a new association of carbapenemics with beta-lactamase inhibitors that is already in clinical development (TANGO studies) to treat ESBL and carbapenemase infections of classes A, B and D
d) A new antifungal is in development, VL-2397, which has a promising mechanism of action, since it acts on a Sit1 membrane transporter that is not expressed by mammals, with the corresponding lower toxicity

7. In relation to the objectives 90-90-90 (90% of the patients with HIV infection diagnosed, 90% of the patients in treatment, 90% of the patients with suppressed viral load) of UNAIDS, which is the current state of fulfillment of these objectives

a) 80-20-10
b) 70-50-40
c) 90-80-70
d) 50-30-15

8. Rates of viral suppression (<50 copies of HIV-RNA) in patients without previous treatment in the current trials of the new combination Bictegravir / TAF / FTC at 48 weeks is:

a) 92%
b) 80%
c) 50%
d) 30%

9. Which of the following is a combination and correct dosage of injectable antiretroviral drugs?

a) AZT / 3TC / Efavirenz every 3 months
b) Dolutegravir / Rilpivirine every 6 months
c) Cabotegravir / Rilpivirine every 1-2 months
d) Doravirin / Flavirin / 3TC every 6 months

10. Delafloxacin is, in your opinion:

a) An exclusive drug for Gram-negative
b) A more active drug against *P. aeruginosa* than ciprofloxacin
c) A quinolone with activity against methicillin-resistant *Staphylococcus aureus*
d) A drug with a great impact on QT
e) A specific drug against *Enterococcus* spp

11. Cefiderocol is:

a) Active against *P. aeruginosa*
b) A siderophore cephalosporin
c) An active drug against *Stenotrophomonas* spp
d) A drug with a coverage against Gram negative greater than 90%
e) All of the above

12. Lefamulin is:

a) A pleuromutilin
b) A new cephalosporin
c) A urinary antiseptic
d) None of the above is true

13. Compliance with the hand hygiene instructions is conditioned by

a) Workload
b) Availability of alcoholic solutions
c) Time available
d) All the previous ones

14. Contact precautions are one of the key elements to prevent horizontal transmission of multi-resistant microorganisms in all of the following scenarios except:

a) Patients colonized or infected by MRSA
b) Patients colonized or infected by *C. difficile*
c) Patients colonized or infected by carbapenemase-producing enterobacteria
d) Patients colonized or infected by ESBL-producing *E. coli*

15. Programs to optimize the use of antimicrobials can help achieve the following objectives

a) Decrease the colonization infection rate by multiresistant
b) Improve clinical outcomes (mortality, average stay) of patients with infections.
c) Promote the use of cost-effective treatments
d) All the previous ones

16. Isavuconazole has activity against ...

a) *Mucor* sp
b) *Aspergillus* sp
c) *Cryptococcus* sp
d) All

17. The echinocandins ...

a) They can not be used in catheter-related sepsis
b) They are useful as empirical treatment in ICU patients with persistent fever
c) Could be used in candidemias of urinary origin if the focus is drained
d) The three previous answers are false

18. Say which of the following associations is false:

a) Anti-TNF and increased risk of tuberculosis
b) Inhibition of IL-17 and increased mucocutaneous candidiasis
c) Tyrosine kinase inhibitors and predisposition to fungal infection
d) IL12 inhibitor and increased risk of cryptococcosis

19. Indicate the correct answer in relation to carbapenemase-producing enterobacteria (CPE) in Spain

a) The most prevalent are the NDM producers
b) The most prevalent are the OXA-48 producers
c) They are not important in the hospital environment
d) They are at the moment very infrequent

20. Point out the correct answer about extremely drug resistant *Pseudomonas aeruginosa* isolated in Spain

a) It has a polyclonal structure not dominated by high-risk clones
b) Most strains with carbapenemase are of KPC type
c) It is associated with widely distributed high risk clones
d) The extremely resistant phenotype has emerged since 2015

21. Indicate the correct answer. Resistance to colistin in *Escherichia coli* and *Klebsiella pneumoniae* associated with the *mcr-1* gene

a) It is produced exclusively in multi-resistant isolates
b) It has been found both in isolates of hospital origin and extrahospitalaries
c) It has not been isolated for the moment in high risk clones
d) It is always of a very high level

22. According to the study developed in several Spanish hospitals about vaccination against influenza virus in carriers of solid organ transplantation, indicate the correct

a) The study shows a lower incidence of influenza in vaccinated
b) The study shows that administration of two doses of vaccine produces a greater immune response than vaccination with a single dose
c) The study shows that vaccination with three doses, with intervals of 4 weeks between them, is superior to the administration of one or two doses of the vaccine
d) All of the above are false because no pattern has been shown to obtain better results than single-dose vaccination

23. According to the international study on risk factors for early aspergillosis (first 6 months after transplantation) in kidney transplant carriers, which of the following is not a risk factor for this fungal infection?

a) Diagnosis of COPD prior to kidney transplantation
b) Delay of graft function (need for hemodialysis after transplant)
c) Double kidney transplant
d) Bacteremia after kidney transplantation

24. According to the international study on invasive pulmonary aspergillosis in renal transplantation, patients present higher mortality when

a) They do not receive treatment with voriconazole
b) Lung involvement is bilateral at the time of diagnosis
c) Aspergillosis occurs in the first months after kidney transplantation
d) All of the above are true

25. Regarding the administration of antibiotic therapy in extra-hospital medicine, we could say that without a doubt:

a) Mortality decreases
b) The hospital stay decreases
c) Decrease the need for admission to the Intensive Care Service
d) None of the above is sufficiently demonstrated

26. Regarding the usefulness of qSOFA and SIRS, indicate the one that seems most correct.

a) SIRS has a greater capacity to identify the infected patient than the qSOFA.
b) SIRS has a greater capacity to identify the patient with poor short-term prognosis than the qSOFA.
c) qSOFA has a greater capacity to identify the infected patient than SIRS.
d) None of the above is true

27. The steps to follow to adequately evaluate the patient with suspected infection are.

a) Determine the focus of the infection, identify the need to control the focus in an interventionist manner, evaluate the immunological situation and evaluate the presence of shock.
b) Carry out a qSOFA and if it is greater than 2 make a SOFA
c) Perform a SIRS, a qSOFA, a SOFA
d) Remove blood cultures and put an antibiotic

28. Before a 30-year-old patient who consults in the emergency room for a respiratory episode with fever of 39 ° C, leukocytosis of 20,000 cels / mm^3 and has a lobar condensation on the chest radiograph, point out the correct option

a) I must wait to know the value of PCT before starting antibiotics
b) I will only start antibiotics if it has a lactate> 4 mmol / L
c) I will only start antibiotics if you have a positive antigenuria for pneumococcus
d) I must initiate empirical antibiotherapy

29. Mark the correct answer

a) PCR generates confusion in clinical decisions and should stop being requested
b) New definitions of sepsis recommend not using biomarkers in clinical decision making
c) Some biomarkers have demonstrated their usefulness both in the diagnosis of sepsis and in the prognosis
d) The best biomarker for the diagnosis of bacterial infection is lactate

30. Regarding the usefulness of biomarkers in the management of infection, point out the true answer

a) PCT has shown in several clinical trials its utility to reduce antibiotic treatment with safety
b) MR-ProADM identifies seriously ill patients
c) Lactate is necessary for the diagnosis of shock according to the new definitions of sepsis of 2016
d) All are true

31. It is not true what:

a) In the centers where prophylaxis with quinolones is carried out in the TPH, the incidence of resistance is higher
b) Inappropriate empirical treatment in patients undergoing HSCT is associated with higher mortality
c) In bacteremia due to ESBL-producing Enterobacteria, beta-lactams with beta-lactamase inhibitor can be used if they are sensitive in vitro
d) In febrile neutropenia, the empirical antibiotic tto must be followed until the neutrophil count is recovered

32. Regarding pneumonia due to *P. jiroveci* (NJP) in onco-hematological patient

a) It is an isolated phenomenon in these patients
b) The CD4 figure below 200 indicates the start of prophylaxis
c) Doses of intermittent corticosteroids and lower than those of 20 mg / d / 4s constitute a risk factor for NJP
d) Prophylaxis is not indicated in patients who receive PD1 and have colitis that requires treatment

33. Regarding new drugs in the treatment of onco-hematological patients and the appearance of infections

a) The use of PD1/PD L-1 correlates with an increase in opportunistic infections
b) Ibrutinib correlates with a greater number of IFI especially in association with steroids
c) Idelalisib is associated with a higher frequency of bacterial infections
d) PI3K in the oncological patient are associated with a higher incidence of NJP

34. In immunosuppressed patients or patients with cancer, we would expect a clinical-radiological presentation in the form of a stroke, or cerebrovascular accident (CVA), with a series of possible microbial etiologies, with the exception of one of the following. Point it out

a) VVZ (Varicella-zoster Virus)
b) CMV (Cytomegalovirus)
c) *Mucor* spp.
d) VHH-6 (Human herpes virus type 6)

35. In the treatment of invasive fungal infections (IFI) of the immunosuppressed CNS, whether caused by filamentous or yeast-like fungi, it is important to use antifungal drugs with the best possible penetration and passage of the blood-brain or hemato-licuoral barriers, to times in combined use; this fact discourages the use of one of them

a) Azoles such as fluconazole and voriconazole
b) Flucytosine
c) Echinocandins such as Caspofungin
d) Amphotericin B

36. Development of Immune reconstitution inflammatory syndrome (IRIS), an old paradoxical reaction, has been observed amog different types of inmunosupression, not only in HIV patients. Its phenomenon is especially serious when affects to CNS. Apart from tuberculosis, which of the following agents has also been related to IRIS?

a) *Cryptococcus neoformans*
b) JC Virus
c) *Treponema pallidum*
d) All the previous ones

37. The microorganism that most frequently causes infections associated with biomedical devices is

a) *Staphylococcus aureus*
b) *Candida albicans*
c) *Staphylococcus epidermidis*
d) *Escherichia coli*

38. The antifungals with greater activity against biofilms of *Candida albicans* are:

a) Azoles
b) Polyenes
c) Echinocandins
d) Terbinafine

39. The treatment of a candidaemia related to a tunneled central venous catheter should include?

a) The removal of the catheter
b) Antifungal lock with an echinocandin
c) Antifungal lock with amphotericin B
d) Combined systemic antifungal treatment

40. With regard to the diagnosis of *Clostridium difficile* infection, indicate, from the following statements, which one is correct

a) Patients with positive free toxin have *C. difficile* disease while those diagnosed by PCR are simply colonized
b) "Control tests" should not be done as patients treated for a *C. difficile* infection because they can continue to show positivity for *C. difficile* diagnostic tests even though they are clinically cured
c) If there is a suspicion of recurrence of *C. difficile* infection, it is not necessary to repeat the diagnostic tests
d) Treatment should be prescribed against *C. difficile* in any immunosuppressed patient who is detected positive for *C. difficile*

41. An 82-year-old patient suffered a first serious episode of *C. difficile* infection and was treated with vancomycin. He answered slowly but finally was asymptomatic. A month later he enters for a second episode, serious. You would consider using fidaxomicin for one of the following reasons

a) Because the risk of recurrence is reduced compared to what would be if metronidazole or vancomycin were used
b) Because it is possible that resistance to vancomycin used in the previous episode has developed
c) For the risk of absortion and toxicity of vancomycin by repeated cycles with said antibiotic
d) Because a lower risk of death due to *C. difficile* has been demonstrated with the use of fidaxomicin

42. The prognosis of ICD in a hospital can (and should) be improved by certain strategies. Point out the incorrect

a) Encourage the use of combination therapy (metronidazole + vancomycin)

b) Develop a faecal transplant program (transfer of faecal microbiota)

c) Use fidaxomicin or Bezlotoxumab (associated with an antibiotic against C. difficile) in patients with a high risk of recurrence

d) Early identification of the most serious patients to be seen by an expert surgeon

Correct answer sheet

VIII Updating Course of Antimicrobials and Infectious Diseases 2018. Correct answers

	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
16				X
17			X	
18				X
19		X		
20			X	
21		X		
22		X		
23			X	
24				X
25				X
26	X			
27	X			
28				X
29			X	
30				X
31				X
32			X	
33		X		
34				X
35			X	
36				X
37			X	
38			X	
39	X			
40		X		
41	X			
42	X			