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Introduction

Update in Infectious Diseases 2019

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ABSTRACT

The IX Updating Course of Antimicrobials and Infectious Diseases included a review of the main issues in clinical microbiology, epidemiology and clinical aspects for a current approach of infectious pathology. The present introduction summarizes about the most important meetings related to infectious diseases during 2018 (ECCMID, IAS, ASM and ID Week). In addition, the course provides a practical information to focus on nosocomial infection models, with immunosuppressed patients or complex multidrug-resistant pathogens. The closing lecture of this year reviewed the infection during donation process.

Key words: Clinical Microbiology and Infectious diseases, current concepts.

INTRODUCTION

Last February, the IX 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 57/094976.9/18, www.infeclinico.es) 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 450 professionals of all specialties related to infection, the teachers made an update of the most relevant aspects on clinical microbiology and infectious diseases.

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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 be able to contrast the results. Revisions have been grouped under 3 headings to guarantee a greater educational character. First of them was an update in infection related meetings during 2018, and we have selected the European Congress of Clinical Microbiology and Infectious Diseases or ECCMID, the American Society of Microbiology Microbe or ASM Microbe 2018, the International AIDS Society meeting or IAS 2018 and the Infectious Diseases Week or ID Week 2018. For the second section, a practice approach of epidemiology and clinical management of nosocomial infections. For the last heading an update in management of immunosuppressed patients. The closing lecture of this year reviewed the infection during donation process.

UPDATE IN INFECTION RELATED MEETINGS DURING 2018

Dr. Emilia Cercenado tried to summarise the ASM Microbe 2018, which took place in Atlanta (GE), focusing on the most important aspects in terms of new techniques of microbiological diagnosis that have improved the diagnosis of infectious diseases, resistance to antimicrobials and new antibiotics. There were 24 plenary sessions, 84 symposia, 25 meet-the-expert sessions, 20 workshops, and more than 2000 abstracts were presented. Among all the new technologies that have been developed for the diagnosis of infections, Dr. Cercenado highlighted the technique ATR-FTIR, a technique to quickly obtain the fingerprint of the whole-organism to allow bacterial identification and discrimination of different subspecies [1]. She also talked about magnetic resonance for detecting microorganisms in clinical samples, as well as laser dispersion for the detection of microorganisms in organic fluids and in the screening of urine samples for the diagnosis of ITUs. Finally, she mentioned Microfluidic [2] and genome sequencing as

very promising techniques. Regarding resistance to antimicrobials, Dr. Cercenado presented the study where the transferable gene *mcr*-1 that confers resistance to polymyxins was first described in China in 2015 [3]. In another study, presented at ASM Microbe, the presence of a chromosomally transferable *mcr*-5 gene was first described in a clinical isolate of *P. aeruginosa* resistant to colistin in the United States. She also dealt with the resistance to carbapenems among *P. aeruginosa* isolates, which, although it is generally chromosomally encoded, several studies presented at the ASM Microbe conference describe an increase in the appearance of plasmid resistance and transferable carbapenem between this species. Finally, new families of antimicrobials are emerging with new mechanisms of action, as well as new drug associations, which are active against multiresistant bacteria. She stressed odilorhabdins; the novel siderophore cephalosporins, such as GT-1; the new tetracycline eravacycline; and other antibiotics or antifungals recently marketed (delafloxacin; plazomycin, rezafungin).

The last European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) which took held in Madrid (Spain), last April 2018, focused in three different aspects: microbiology diagnosis, resistance to antimicrobials, and new antimicrobials. All of this microbiology diagnosis techniques were summarized by Dr. García-Lechuz [4]. The (MALDI-TOF MS) is a primary method [5] for the identification of microorganisms, that only requires little amount of bacteria and allows high-throughput (Rodriguez-Sánchez B, et al; P2236). An interesting experience in identification of non-tuberculous Mycobacteria isolates was presented by Rodriguez-Sánchez B, et al; P2405. Another technique like PCR-MALDI could replace current real-time PCR technology detecting bacterial (Green J, et al; P2376) and fungal species. Lastly, there were some experiences with Sepsis Flow Chip (SFC) assay, based on multiplex PCR and low-density DNA arrays, detecting Gram-positive and Gram-negative bacteria and fungi, and, in the same assay, the most common antibiotic resistance genes [6]. The AMR Direct Flow Chip assay (Galiana A, et al; P2288) detects the main genetic resistance determinants in a single step. This assay was compared to next-generation sequencing (NGS) techniques and showed sensitivity and specificity values close to 100%.

The immunochromatographic tests (ICT) are a good option and has been recently developed for Carbapenemase-producing *Enterobacteriaceae* (CPE) detection from cultures on solid media. This can help to rapidly identify patients with CPE BSI (Bloodstream infections), optimize the treatment of patients and reduce the mortality. The NGS analyze the entire human genome or to sequence thousands of genomes (Vincent AT et al, 6). Sanger sequencing and NGS can be used for detection of HIV drug resistance mutations (García-Arata MI, et al; P1902). With NGS you can have the results in three labor days and for a low price. The findings made NGS an effective new strategy and a useful tool in the detection of HIV resistance.

The antimicrobial resistance was also reviewed by García-Lechuz. The multidrug-resistant Gram-negative bacteria is a worldwide problem. Colistin is one of the last resort antimicrobials for the treatment of infections caused by multidrug-resistant Gram-negative bacteria but in recent years, the resistance is increasing, [7, 8]. In a study presented by Mendes AC, et al (P0417) there were isolates of *Klebsiella pneumoniae* producing KPC-3 and mcr-1, surviving after polymyxin treatment in vitro and in vivo. One study analyzed the impact of the mechanism of resistance to carbapenems in Gram-negative on mortality. The highest crude mortality was observed in *K. pneumoniae* (KPC and OXA-type had higher mortality than metallo-betalactamases (MBL)) followed by *Acinetobacter baumannii* (OXA-type was higher than MBL) and *Pseudomonas aeruginosa*. (Pezzani MD, et al; P1052).

Emergence of ceftolozane-tazobactam resistance is caused by structural mutations in intrinsic (AmpC) or acquired (OXAs) beta-lactamases. Other resistance mutations include specific large chromosomal deletions and PBP3 mutations (Oliver A; S0387). Ceftazidime-avibactam resistance appear after mutation in KPC-2 or KPC-3 (Humphries RM; S0386). Animals like cows, pigs, veals, calves and poultries can act as reservoirs of antimicrobial resistance genes. Colistin-resistant *E. coli* from animals may represent a potential risk to human health (Lei L, et al; O1050). Among new antimicrobial agents was important to mention the FDA approved delafloxacin, meropenem-vaborbactam and other antimicrobial agents are in End-stage clinical development like cefiderocol, eravacycline, imipenem-relebactam, omadacycline or plazomicin.

There are many studies, clinical trials, prospective studies to show us the new antimicrobial agents' effect. For example, the phase III clinical trials IMPACT 1 and 2, analyzed efficacy of oral cadazolid versus vancomycin. Cadazolid showed no inferiority and was safe, well tolerated and could potentially be an alternative therapy for *Clostridium difficile* infection. In the study REVIVE-2 (O0424) iclaprim was non-inferior to vancomycin. In the OASIS-2 phase III clinical trial (O0425), Omadacyclin was non-inferior to twice-daily oral linezolid in the treatment of adults with skin and soft tissue infections. Against multidrug resistant Gram-negatives, the clinical trial (RESTORE) (O0427) compares imipenem-relebactam versus colistin and imipenem for *Pseudomonas* spp and *Klebsiella* spp infections. The patients treated with imipenem-relebactam had a favourable overall response. In the other side, in TANGO II study, meropenem-vaborbactam was associated with increased clinical and microbiologic cure. The new agent cefiderocol, has a great activity against carbapenem-resistant *Enterobacteriaceae* and meropenem-resistant *Pseudomonas* spp, showed no inferiority in the phase III APEKS trial in complicated urinary tract infection cUTI. The antipseudomonic agent, murepavadin, showed great activity against *Pseudomonas* spp in HABP/VABP phase II clinical trial. Eravacyclin showed similar results than meropenem or ertapenem in the IGNITE trials (O0421). Related to community-acquired infections, lefamulin (phase III clinical trial LEAP-1) and omadacyclin (phase III clinical trial OPTIC) were compared with moxifloxacin, with non-inferiority results including the PORT risk class III to V (P0276). The Merino trial, comparing piperacillin-tazobactam and meropenem for treating blood stream infections, showed no differences in microbiological eradication and test of cure between the two groups

but the difference in mortality rate was significantly lower in meropenem branch.

ID Week is an annual scientific meeting of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association and the Pediatric Infectious Diseases Society. ID Week 2018 was held in October in San Francisco. Dr Emilio Bouza made a selection of symposia, reunions and abstracts that drew his attention. He pointed out the conference was focused on medical education and updating on the attendees and the event on topics like adult infectious disease (ID), pediatric ID, global ID and HIV. Dr Bouza focused attention on some topics from the 74 symposiums: antibiotics policy, new antimicrobials, situation of human microbioma and the outstanding increase of apiaceous use with associated infections. Among the new antimicrobial in research, he mentioned tetracyclines, inhibitors of beta lactamase and a new antifungal, ibrexafungerp, with a new action mechanism.

In the communications section he selected those issues related to *S. aureus*, *C. difficile* community-acquired infections, its overdiagnosis in colonized cases, control of requests trough stewardship, the value of quantifying the PCR tests for *Clostridium difficile* infection (CDI) by evaluating the positivity cycle of the amplification curves, decreasing of relapses with bezlotuxumab, faecal transplant with capsule, Gram-negative bacterial infections and ceftolozano-tazobactam susceptibility *in vitro* of *K. pneumoniae* and *Pseudomonas aeruginosa*, advantages of stewardship, rational antifungal treatment applying T2 Candida testing, asymptomatic influenza, baloxavir marboxil in high risk influenza patients, aspergillosis among patients with influenza, injection opioid drug use as an emerging risk factor for candidemia and *S. aureus* bacteremia. In the conclusions, Dr. Bouza called attention on a more representative presence of infectology over microbiology, the low amount of basic science, and the American opiates abuse concerns.

Last conference was the 22th International AIDS Conference and was summarized by Dra Núñez-Orantos. In this conference Dra Nuñez highlighted the GEMINI and DIAMOND studies and in the second time the PARTNER study. GEMINI-1 and -2, published by Cahn et al [9], showed that the virologic efficacy of 2-drug regimen of Dolutegravir (DTG) plus Lamivudine (3TC) was non-inferior to 3-drug regimen of DTG plus Emtricitabine (FTC)/Tenofovir disoproxil fumarate (TDF) in treatment-naive patients at Week 48. The main objective was to establish the percentage of participants with a viral load below 50 copies/ml at 48 weeks after starting the study. In conclusion, a dual therapy with 3TC + DTG in naive patients could be an alternative to a triple therapy based on TDF + FTC + DTG. DIAMOND Study was a prospective multicenter study evaluating Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) in a rapid initiation model of care over 48 weeks. In this trial, a high proportion of patients using D/C/F/TAF achieved HIV-1 RNA <50 copies/ml. No patients discontinued treatment. The results of the mean HIVTSQs score indicated a high level of satisfaction. These findings suggest that D/C/F/TAF should be considered an adequate option of treatment.

The PARTNER2 study shows in serodifferent men having sex with men (MSM) couples reporting condomless sex when HIV-positive partner virologically suppressed, Rodger A et al [10], Bavinton BR et al [11]. The main finding of the study was that no within-couple HIV transmissions were observed among 783 serodifferent MSM couples who reported condomless sex while the HIV-positive partner was receiving suppressive ART. This data shows that the risk of HIV transmission from an HIV-positive partner who has undetectable HIV-1 RNA is effectively zero. The PREVENIR study, Molina et al. [12] showed the real-life data of the PrEP (pre-exposure prophylaxis) application in Paris. At an average follow-up of 7 months, the incidence of HIV in both groups was 0, and it was estimated that 85 HIV infections had been prevented.

UPDATE IN NOSOCOMIAL INFECTION

The acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp) [13] was coined by US researcher Louis B Rice to designate a particular group of microorganisms that have been mainly associated with nosocomial antimicrobial resistance. In his conference, Dr. Cantón exposed data from the European Antimicrobial Resistance Surveillance Network [EARS-Net] that show an alarming increase of resistance among the ESKAPE bugs in Europe in the recent years [14], with a huge impact in mortality and economic cost of infections caused by these organisms. He focused his speech in the current situation in Spain, particularly in carbapenem resistance; emphasizing the emergence, persistence and rapid dispersion of this resistance mechanism, with a dominance of OXA-48 producing *K. pneumoniae* isolates [15]. Dr. Cantón pointed out the increased number of colonized patients 3 and the presence of multi drug resistance high-risk clones as the main factors contributing to the emergence and spread of carbapenemase producing *Enterobacteriaceae* throughout the country. To end up, he highlighted the appearance of resistance to new β-lactam–β-lactamase inhibitor combinations, showing interest in a recently described KPC mutation that confers resistance to ceftazidime-avibactam while restoring carbapenem susceptibility [16], stressing the need of developing new antibiotic compounds.

Relevant aspects of antibiotic selection in the treatment of acute invasive infections by *P. aeruginosa* were reviewed. Regarding the MIC of antibiotics, it was stated that for the treatment of severe or high bacterial load infections, produced by microorganisms exhibiting MIC ≥4 mg/L of the β-lactam, only elevated doses administered by continuous or extended infusion reach free antibiotic concentrations exceeding 4-times the MIC [17] and that for the aminoglycosides, the greatest efficacy for a treatment is obtained when Cmax/MIC ≥10 [18]. It was also commented that in infections with high bacterial load, an early and rapid ≥ 2 log10 CFU/mL decrease produced by the antibiotic treatment might decrease bacterial density allowing an optimal contribution for microorganism eradication [19]. And to avoid selection of resistant mutants,

antibiotics [like aminoglycoside, ciprofloxacin or levofloxacin] associated with the β-lactam during the first 48-72 h, should be administered at doses achieving concentrations over the corresponding MPCs. The authors exposed that in certain infection sites, the possibility of directly introducing the antibiotic into the infectious foci using the inhalatory, intrathecal or other routes to increase antibiotic concentration in the foci should be considered. The relevance of early administration of an appropriate antibiotic treatment when the infection presents clinical or biological severity criteria, the patient suffers important immunodepression or comorbidities or has advanced age was also highlighted [20]. Finally, the current clinical experience with monotherapy and combination therapy for the treatment of acute invasive infections by *Pseudomonas aeruginosa* was presented.

Doctor Azanza warned in his presentation about the need to review the posology of most anti-infectives. In the past, dosing guidelines were chosen by selecting those with the ability to exceed MIC and based on tolerance criteria. The discovery of the importance of PK/PD relationships highlights the importance of reviewing these posological guidelines. Dr. Azanza talked about the three types of PK/PD relationships that have been established for antibiotics. The first one is the concentration dependent model, which uses the inhibitory coefficient (Cmax/MIC) as a reference parameter. This coefficient indicates that the effect of a drug fundamentally depends on the coefficient between the highest concentration reached and the minimum effective concentration. The drugs that belong to this group show that the higher administrated doses, the greater activity is presented, without the administration interval being especially relevant. Consequently, it is recommended to administer one daily dose. An example of this group of drugs would be aminoglycosides, to which he referred in a study on nephrotoxicity induced by aminoglycosides [21].

The second PK/PD model uses as a defining parameter the AUC / MIC, which takes into account both the MIC and the time period in which the concentration values remain above it. These antibiotics must be administered in a dose that will generate the highest possible plasmatic concentration, and at intervals that avoid the presence of subinhibitory concentrations. This group would include vancomycin, to which he referred in a study on vancomycin-induced nephrotoxicity [22]. The third and last model is the time-dependent model, based only on the time of effectiveness, the time in which the plasma concentration remains above the MIC. The choice of dosage regimen is simple for drugs with high half-life elimination, such as beta-lactams. During his presentation, Dr. Azanza highlighted a study on pharmacokinetics and pharmacodynamics in beta-lactams [23]. In this PK/PD model, the problem relies on the administration of drugs with short half-lives (less than 2h), which will require many daily endovenous doses.

Catheter-related bloodstream infections (CRBSI) is a common cause of nosocomial infection associated, resulting in substantial morbidity, mortality, increased length of hospital stays and higher health-care costs.

Dr. Garnacho focused her presentation on giving updated recommendations and key aspects concerning to the diagnosis and management of adults with CRBSI, based on a review of the new clinical practice guidelines for the management of this entity, recently published by the Spanish Society of Infectious Diseases an Clinical Microbiology (SEIMC) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) (24). Some aspects were summarized by Dr. Garnacho, emphasizing the fact that an accurate diagnosis of CRBSI becomes essential because of the serious consequences associated with inaccurate or failed diagnoses.

The guidelines define the clinical characteristics, along with other factors, to establish a clinical suspicion and initiate a microbiological diagnosis, as well as, indicating the conditions needed to consider the CRBSI as complicated. The guidelines also highlight the recommendation that a catheter culture must only be obtained when a CRBSI is suspected, thus avoiding unnecessary cultures [25]. Catheter removal is the most suitable approach for the diagnosis of CRBSI at least in the critical care setting. However, withdraw or replacement of a suspicious central venous catheter may not be feasible in many cases, so then conservative techniques may be employed in the diagnosis. In this regard, Dr. Garnacho made a summary of the main diagnostic methods for CRBSI, such as semiquantitative or quantitative culture of catheter tip, quantitative or differential time to positivity blood cultures, among others. In addition, molecular-based rapid diagnostic testing, which has evolved recently for the early identification of microorganisms involved in bloodstream infections, are contemplated in the cited guidelines due to its usefulness for improving the diagnosis, especially in patients under antibiotic therapy [26, 27]. Regarding treatment, Dr. Garnacho highlighted the importance of choosing the empiric anitimicrobial agents based on an assessment of the risk factors for infection, the severity of the clinical picture and the likely pathogens based on local ecology and catheter site of insertion, as well as the importance of oral sequencing treatment.

Sepsis, that can be defined as a life-threatening organ dysfunction caused by a deregulated host response to infection, is the major cause of mortality from any infectious disease worldwide [28]. Dr. Del Pozo described the importance but also the limitations and challenges, of applying antimicrobial stewardship programs to sepsis. The goals of antimicrobial stewardship are to achieve optimum clinical outcomes, and to ensure cost effectiveness and minimum unintended consequences, including toxic effects, selection of pathogenic organisms, and resistance. The combination of inadequate diagnostic criteria for sepsis, with the extraordinary time pressure to provide broad-spectrum antimicrobial therapy is troubling from a stewardship perspective [29]. There are several challenges to face. Firstly, the diagnosis of severe sepsis may be delayed because physicians or nurses may not identify the progression of sepsis, and/or because some patients may not show obvious systemic manifestations of the process. Secondly, patients may have differences in the timing of their presentation and concurrent conditions confounding the diagnosis.

Thirdly, treatment may be delayed once the diagnosis is made [30]. Another aspect to take into account is the microbiological diagnosis. The first 3-6 hours after the clinical suspicion are critical to establish therapeutic measures that improve prognosis. Therefore, a microbiological diagnosis in less than 6 hours would undoubtedly benefit the optimal management of patients. Unfortunately, rapid molecular-based diagnostic tests usually provide little information on antimicrobial susceptibility. Dr. Del Pozo emphasized that despite all the challenges surrounding antimicrobial stewardship programs when we talk about sepsis, they can lead to significant benefits for clinical outcomes, adverse events and costs. This can be done by adhering to local guidelines for empirical therapy, multidisciplinary bedside consultation, optimized antibiotic dosing, and integration of rapid diagnostic techniques in the decision-making process. Nevertheless, there is still a long way to go on this topic.

Clostridium difficile infection (CDI) is the most common cause of nosocomial antibiotic-associated diarrhea worldwide and additionally due the high risk of recurrence (12%-40%) has led to multiple emergency therapies as fidaxomicin (FDX), faecal microbiota transplantation (FMT) and monoclonal antibodies [31, 32]. Dr. Salavert reviewed new strategies for effective prevention of recurrent CDI (rCDI) and he emphasized that FDX compared to vancomycin treatment, was associated with a lower rate (~50%) of second-occurrence relapses 4 weeks after the infection in patients with no prior episode of CDI. Hence, FDX is recommended from the first episode of infection in patients with recurrence risk factors (elderly people, concomitant antibiotic use and severe underlying disease) [33], but due to its higher cost, this use is reserved for patients with first or later recurrences. Otherwise, FMT has a rate of cure of rCDI about 90% when associated to antibiotic cessation and may be offered to patients with rCDI who have had at least two recurrences, or one recurrence and risk factors for further episodes [34]. However, in Spain it is still not a routine procedure and the potential benefit of FMT in primary CDI remains uncertain. Finally, he explained that a new approach to the prevention of rCDI is the administration of monoclonal antibodies *against C. difficile* toxin B. Bezlotoxumab is the first of this kind and is currently approved for the prevention of rCDI in patients on treatment for CDI and who are at high risk for recurrence [35]. In the near future, some of new molecules (cadazolid, ridinilazole, auranofin and thuricin CD) might be effective alternatives to fight against CDI and prevent more effectively rCDI.

UPDATE ON THE INFECTION OF THE IMMUNOCOMPROMISED PATIENT

Febrile neutropenia (FN) is a common complication in patients with hematologic malignancies receiving chemotherapy and is associated with high morbidity and mortality. Infections caused by multidrug-resistant bacteria represent a therapeutic challenge in this high-risk patient population, Dr. Gudiol reviewed the most relevant issues included in the recently published Consensus Document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Association of Hematology and Hemotherapy (SEHH) on the management of febrile neutropenia in patients with hematologic malignancies [36]. Stratification of patients should include validated models such as the MASCC index score [37]. Many factors should be considered when choosing empirical antibiotic treatment in patients with FN. These include the risk of infection associated with the severity of neutropenia, possible focus of infection, clinical manifestations (e.g., hypotension, sepsis, septic shock), local epidemiology, previous infection or colonization by multidrug-resistant organisms, previous use of antibiotics, and presence of allergies and potential toxicities. Antibiotic treatment should be selected and modified according to the suspected clinical focus of infection). Furthermore, reducing the exposure to unnecessary antibiotic is a cornerstone in the fight against antimicrobial resistance.

In patients with FN and clinically documented infection, antibiotic treatment can be discontinued when clinical signs and symptoms of infection have resolved and the patient remains afebrile for at least 72 hours [38], avoiding the standard approach of maintenance until neutrophil recovery. Gram-negative bacteria are the leading cause of infection in onco-hematological patients with febrile neutropenia, and emergence of multidrug resistance among these organisms is a matter of concern [39]. The use of a β-lactam with activity against P. aeruginosa is recommended, in monotherapy or in combination with another regimen. Special attention was given to the treatment of extended-spectrum betalactamase-producing *Enterobacteriaceae* (ESBL-E). Beta-lactam and beta-lactam inhibitor combinations (mainly piperacillin-tazobactam) should be considered as carbapenem-sparing alternatives for the treatment of low-risk patients who do not have a high-inoculum infection and present without severe sepsis or septic shock [40]. Extended infusion is strongly recommended [41]. Patients considered to be at low risk for complications can be treated with oral antibiotics and outpatient follow-up after 48-72 hours [42].

In her presentation, Dr. García-Vidal reviewed relevant aspects related to chemoprophylaxis of mould infection. Firstly, she explained that IFI prevention should be made a priority objective in at-risk patient, such as hematopoietic stem cell transplant recipients (HSCT), solid organ transplant recipients (SOT) and patients with hematological malignancies, all those with acute myeloid leukemia. In addition to these classic risk groups, the speaker exposed that the use of novel treatments like immunomodulatory and immunosuppressive agents has increased the risk of IFIs in patients with chronic lymphoproliferative disorders [43]. Secondly, Dr. García-Vidal stated that clinical guidelines for the management of invasive diseases caused by Aspergillus, recently published, recommend posaconazole as a first line antimould prophylactic [44]. In addition, she commented that the pharmacokinetic and pharmacodynamic properties of isavuconazole offer potential for use in fungal prophylaxis, salvage therapy or in combined regimens [45].

Latent infection in patients receiving biological therapies was reviewed by Dr. Fernandez-Ruiz. First, he highlighted the most prevalent latent infection in our area is Tuberculosis, in which the host's adaptive immune system ultimately depends on the dynamic equilibrium between pro-inflammatory and anti-inflammatory cytokines. TNF-α cytokine, exerts a major role in the structural maintenance of tuberculous granulomas, and theoretically the use of agents targeting tumor necrosis factor (TNF-α) increase the risk of reactivation of latent tuberculosis infection (LTBI), and progression to active disease [46]. Nevertheless, it is noteworthy that no cases of tuberculosis were reported in the randomized clinical trials (RCTs), despite the lack of specific risk-minimization measures in these studies [47]. Post-marketing follows up, reported by the FDA, revealed the first cases of adverse events, allowing to delineate the risk of LTBI reactivation in patients receiving TNF-α-targeted therapies [48]. Notice that such risk increase is not uniform across different agents: the use of etanercept is consistently associated with a lower incidence of LTBI reactivation as compared to monoclonal antibodies targeting TNF-α [49]. Moreover, the risk of active tuberculosis also varies according to patient age (with higher incidence in older groups) and the background rate of LTBI in the overall population. Finally, he described different strategies for screening latent tuberculosis infection: the tuberculin skin test (TST) and the interferon (IFN)-γ release assays (IGRAs), the last one has the advantage of better reproducibility and specificity than TST. There is general consensus in performing both tests and, eventually, a chest X-ray examination prior to the initiation of TNF-α-targeted. However, the optimal screening sequence to avoid an unacceptable number of false-positive results is still not well established. Regarding to patients diagnosed with LTBI, tuberculostatic treatment is mandatory and the administration of the anti-TNF-α agent should be delayed for 30-60 days [50]. A 6 to 12-month course of isoniazid monotherapy (300 mg daily) remains as the first-line option, but alternative regimens have been successfully tested in recent trials.

Dr Fernández-Ruiz made a brief mention about reactivation of viral pathogens able to establish chronic or latent infection within the host, like Hepatitis B viral infection. This balance between the host's immune surveillance and the virus can be disrupted by immunosuppressive therapy, leading to viral replication that can evolve into life-threatening hepatitis. Mayor risk is clearly associated with the use of anti-CD20 monoclonal antibodies in HBsAg-positive patients, and lower substantially risk is observed among HBsAg-negative/anti-HBc-positive patients ("hidden infection") [51].

Closing Conference was presented by Dr. Len, who provided a general up-to-date overview about the revelation of transplantation, the difference between demand and supply and the need of having a look to marginal donors, who could transmit infections to their recipients. Although the number of patients on the waiting list has more than double since 1998, the number of transplants has increased by only about 30% [52]. In any case, the rigorous examination of the donor to detect latent and active infections is essential to prevent the involuntary use of inadequate organs, to optimize the prophylaxis directed against the infection, the preventive therapy or the surveillance measures of infections after transplant. Dr Len analyze two types of transmission of an infection, the expected one, from the donor to the recipient, in which we have prophylaxis or it's controllable, and the unexpected one, where we don't recognize it before the transplant, usually we do not have effective prophylaxis or treatment and, therefore, it has high morbidity and, even, mortality.

Some problems usually block the efforts to prevent unexpected transmission. There are not universal standards for donor evaluation, sometimes it is difficult to differentiate donor-derived infection from the recipient itself, and not all cases of donor-derived infection are published [53]. On the other hand, the causes of unexpected transmission of the infection are, in first place, asymptomatic latent infection not diagnosed in the donor. Considering the current migratory movements, we should not neglect the screening of geographically restricted infections [54] and get a good clinical history of the donor. In second place, absence of diagnosis of active infection as death cause, sometimes because of the lack of early diagnosis and targeted treatment [55]. Without forgetting that the donor may suffer an infectious complication during admission to the intensive care unit, not diagnosed prior to transplantation (e.g. occult bacteremia); and in third place, contamination of preservation fluids [56]. Nowadays, thanks to experience gained, better results are being achieved, and to update information, the Spanish National Transplant Organization, has published a consensus document in collaboration with several scientific societies [57], where in order to advance in prevention of donor derived infection we can act on different directions: improving the screening of infections in donors, with faster, more sensitive and specific tests, involving all the professionals (multidisciplinary team), improving communication between all them (coordination, microbiology, transplant teams) in case of recognizing a risk in a specific donor-recipient procedure, without losing time, in transfer information to the rest of the related transplantations, and finally, with standardized and mandatory notification systems to obtain maximum possible information that allows us to pass from unexpected transmission of the infection to preventable one.

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