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Introduction

Update in Infectious Diseases 2018

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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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