Introduction

Update in Infectious Diseases 2017

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ABSTRACT

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

Key words: Infectious diseases, current concepts

Actualización en patología infecciosa 2017

RESUMEN

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

Palabras clave: Enfermedades Infecciosas, conceptos actuales

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INTRODUCTION

Last January, the VII Updating Course of Antimicrobials and Infectious Diseases was held at the Hospital Clínico San Carlos in Madrid. It is a scientific activity accredited by the Community of Madrid (Commission for Continuing Education of Health Professions at the Community of Madrid, file number 07-AFOC-08829.2/2016, 1.3 credits) and endorsed by the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), the Spanish Society of Chemotherapy (SEQ) and the Madrid Society of Clinical Microbiology (SMMC). Faced with a multidisciplinary assistance composed of more than 600 trainees and young associates of all specialties related to infection, the teachers made an update of the most relevant aspects on bacteriology, mycology and virology.

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

UPDATE IN BACTERIOLOGY

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

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

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

UPDATE IN HIV

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

UPDATE IN MICOLOGY

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

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

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

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

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

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

UPDATE IN MAIN INFECTIOUS SYNDROMES

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

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

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

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

CURRENT APPROACH AND METHODS

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

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

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

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

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

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

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

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

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

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

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

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

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