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CONTENTS

EDITOR´S CHOICE

SCREENING FAILURE THROUGH SONOGRAPHY FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN HIV-INFECTED PATIENTS.

☞ ***Referencia Original:*** Merchante N, Merino E, Rodriguez-Arrondo F, *et al*. Low performance of ultrasound surveillance for the diagnosis of hepatocellular carcinoma in HIV-infected patients. AIDS 2018. En prensa.

The aim of this study was to evaluate the diagnostic capacity of sonography to detect hepatocellular carcinoma (HCC) in HIV-infected patients. To this end, a longitudinal, retrospective, multicentre study was conducted with HIV positive patients diagnosed with HCC in 32 Spanish hospitals between the years 1996 and 2017. The study included all the cases of HCC diagnosed through a biannual sonography screening program. The control group was composed of VHC-monoinfected patients diagnosed with HCC in the period of 2000-2017. The outcome variables of the study were failed detection by sonography, defined as a case of HCC diagnosed in the first 3 months after sonography without signs of HCC, and failed screening program, defined as a diagnosis of HCC initially classified as B, C or D according to the BCLC criteria. The study included 346 patients diagnosed with HCC, with a median age of 49 years (IQR = 46-53), 90% of whom were males (n = 313). Of the total sample, 87% were under antiretroviral treatment at the time of the diagnosis (n = 299), and 74% of these (n = 255) had undetectable viral load. Fifty-four percent of the patients (n = 186) had a sonography before the diagnosis of HCC. The etiology of the HCC was hepatitis C in 223 patients (64.5%), hepatitis B in 29 (8.4%), coinfection by hepatitis C and hepatitis B in 22 (6.4%), hepatitis C and alcohol in 67 (19.4%), alcohol in 4 (1.2%), and another cause in 1 case (0.3%). The proportion of patients diagnosed with HCC after the screening program through sonography was 8.6% in HIV-infected patients (16 out of 186 patients) and 8.6% in HIV negative patients (5 out of 58). The only factor associated with the diagnosis of HCC after failed detection in the screening program was state Child-PT; thus, out of the 16 patients diagnosed with HCC after failed screening system, 5 (31%) were in state A, 6 (38%) in state B, and 5 (31%) in state C, whereas in those patients without failed detection through screening program the distribution was 101 (60%) in state A, 45 (27%) in state B, and 22 (13%) in state C ($p = 0.01$). The proportion of patients diagnosed as B-D according to the BCLC criteria (considered failed detection), was 57% in HIV-infected patients (107 out of 186 patients) and 29% in HIV negative patients (18 out of 62 patients) ($p < 0.001$). The factors associated with failed detection considering the B-D criteria of BCLC were genotype 3 of VHC (20% vs 34%; $p = 0.02$), and undetectable viral load of HIV (78% vs 92%; $p = 0.02$). This failed screening in HIV-infected patients with respect to HIV negative patients resulted in higher mortality at 24 months (40% vs. 65%; $p = 0.038$).

COMMENT: Dr. Antonio Rivero-Juárez

This study shows a high rate of failed detection in the screening program for HCC, which consists in biannual sonography in HIV-infected patients. Moreover, this failure rate was higher in HIV-infected patients than in HIV negative patients, with a detectable viral load of HIV being a factor associated with failure. The solution to this problem is not simple, since there is no consensus to this respect: i) decrease the time between sonographs from 6 to 3 months, and ii) replace sonography with CT scans as the tool for the screening program. What is clear with this study is that the current screening program has a considerable failure rate, which results in a higher mortality of the patients. Future studies are needed to evaluate alternatives to the screening program for cirrhotic patients.

GUEST COLLABORATOR

IS IT POSSIBLE TO TREAT INFECTIONS EFFECTIVELY AND SAFELY THROUGH IVAT IN PATIENTS WHO LIVE BETWEEN 200 AND 700 KM FROM THEIR REFERENCE HOSPITAL?

☞ ***Referencia Original:*** Tan SJ, Ingram PR, Rothnie AJ, et al. Successful outpatient parenteral antibiotic therapy delivery via telemedicine. *J Antimicrob Chemother* 2017; 72:2898-2901.

This is a retrospective, observational study carried out in Australia with 88 cases, from 83 patients (61 males), gathered between 2011 and 2015 in the Royal Perth Hospital. All the antibiotics were administered once per day by the local nursing services, through either slow direct intravenous administration or continuous infusion over 24 hours using an elastomeric pump. Peripherally inserted central catheters were used in all cases. All patients were checked once per week and had a videoconference also once per week with a physician specialised in infectious diseases. The average age was 56 years (RIQ 43-66), and 37% of the patients were diabetic and had a Charlson's index score of 2 (RIQ 1-4). The average distance from the patients' home to the hospital was 288 km (RIQ 201-715), thus, the average distance saved in the trip (to and from)

was 576 Km (RIQ 402-1430). The average duration of the hospital stay before the beginning of the IVAT was 9 days (RIQ 6-16), whereas the average duration of the IVAT was 26 days (RIQ 14-34). A total of 238 home visits were carried out, with an average of 2 visits per episode. The most frequent infections were osteoarticular (75% of cases), followed by skin and soft-tissue infections (10%) and endovascular infections (9%). Five infections were caused by MRSA. None of the cases were caused by ERV or ESBL-producing enterobacteriaceae. The most used antibiotic was piperacillin/tazobactam (31%), followed by flucloxacillin (27%), ertapenem (9%), cefazolin (8%), benzylpenicillin and vancomycin (7%), and ceftriaxone and daptomycin (6%). The recovery/healing rate was 87%, and there were 7 unexpected readmissions (8%). Four of these readmissions were due to progression of the infection, which required surgical treatment, two of them were caused by adverse effects related to the antibiotics, and one was due to occlusion of the catheter.

COMMENT: Dr. Abel Mujal

Home Hospitalization Unit. Department of Internal Medicine. Parc Taulí Hospital Universitari. Sabadell (Barcelona, Spain)

To date, this is the most complete study to evaluate the treatment of accute infections through the combination of IVAT and telemedicine. Western Australia comprises 2.645.615 Km2, four times the size of France, and 1/3 of the Australian population live outside the big cities, which is a challenge for IVAT programs. The article shows that the most frequently treated infections were osteoarticular, followed by those of the skin and soft tissue, which is very common in the articles about IVAT in the Anglo-Saxon world, whereas the most frequent infections in Spain, according to the studies published in this country, are respiratory infections and those of the urinary tract. However, there were surprisingly 8 cases (9%) of infective endocarditis, which are complex processes that usually require a thorough control by the home healthcare team, although in this series the patients recovered satisfactorily. Therefore, the results described by the authors are very favourable and comparable to other studies about IVAT unrelated to telemedicine, with very low rates of adverse effects and unexpected readmissions. This study demonstrates that the combination of IVAT and telemedicine is safe and effective in the management of a large cohort of patients with an infectious disease in a geographically large location. This would be applicable to rural areas far away from the big cities of Spain, where the access to home healthcare is sometimes very difficult due to the orography of the terrain or the lack of proper connections. Telemedicine is already here and it has come to stay. Its implementation throughout the Spanish territory will depend on us and our administrative authorities, and it will surely make our healthcare work easier thanks to its multiple advantages.

COULD THIS FINALLY BE THE FIRST STEP IN THE TREATMENT OF ENDOCARDITIS WITH ORAL ANTIBIOTHERAPY?

☞ ***Referencia Original:*** Iversen K, Ihlemann N, Gill SU, et al.P artial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med* 2018. En prensa.

This is a randomised, non-inferiority, nonblinded, multicentre clinical trial carried out in Denmark. The study included clinically stable adult patients (adequate clinical response, and adequate iv antibiotic treatment for at least 10 days and 7 days for those who had been surgically intervened), with left endocarditis (native or prosthetic) and positive blood culture for Streptococcus sp. (49%), E. faecalis (24%), Staphylococcus aureus SM (22%) and coagulase-negative Staphylococcus (6%). The patients were randomised to either receive the oral treatment chosen according to the causing microorganism or to continue with iv (for MRSA and NCS, both sensitive to penicillins, the options were amoxicillin and fusidic acid, amoxicillin and rifampacin; for penicillin-resistant MRSA and NCS: dicloxacillin and fusidic acid, dicloxacillin and rifampicin, linezolid and fusidic acid, or linezolid and rifampicin; for meticillin-resistant NCS: linezolid and fusidic acid or linezolid and rifampicin; for E. faecalis: amoxicillin and rifampicin, amoxicillin and moxifloxacin, linezolid and rifampicin, or linezolid and moxifloxacin; for Streptococcus sp. with MIC to penicillin <1 mg/L: amoxicillin and rifampicin, linezolid and rifampicin, or linezolid and moxifloxacin; for Streptococcus with MIC to penicillin ≥1mg/L: linezolid and rifampicin, moxifloxacin and rifampicin, or moxifloxacin and clindamicin). The primary outcome variable was composed of and included mortality by all causes, unplanned heart surgery, presence of septic embolisms, or recurrence of the bacteremia with the original microorganism, up to 6 months after the end of the treatment. The margin of non-inferiority was set at 10%. A total of 199 iv patients and 201 oral patients were treated. The primary event occurred in 24 patients (12.1%) in the iv treatment group and in 18 patients (9%) in the oral treatment group [the difference between groups was 3.1% (-3.4-9.6, p=0.40). Four patients were moved from the iv group to the oral group, and they were included in a sensitivity analysis in which non-inferiority was maintained. In addition, the analysis was conducted in specific subgroups of patients (age, sex, diabetes, kidney disease, type of microorganism, surgical treatment or not, affected valve, native or prosthetic). In all the patients, the result was consistent with that of the main analysis, although the study was not designed to reach the necessary potency in these subgroups. In 7 patients of the oral group, the levels of one of the two antibiotics used did not reach therapeutic concentrations; however, the levels of the other

antibiotic with which they were coadministered were appropriate. The primary event did not occur in any of these patients.

COMMENT: Dra. Zaira Palacios Baena

Facultativa Especialista de Área. Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva UH Virgen Macarena, Sevilla.

This study could be the answer to the questions that we ask ourselves daily in the treatment of infective endocarditis. Why is sequential oral treatment effective in some infections and not in endocarditis? The methodology and statistical analysis used were adequate. The study shows a very low mortality in both groups with respect to most of the published series. This means that the target population was different and/or the clinical management and the detection of complications were excellent. Likewise, the average age was lower than that of other European series and, despite the multiple concomitant diseases gathered, the study did not include any data about global comorbidity indices. It is also worth highlighting that the article does not mention any major complication such as lesions in the CNS or kidney failure. The frequency with which surgery was carried out was relatively low (38%), which is another sign of "benignity" with respect to the patients included. Moreover, the study did not included cases of infection caused by meticillin-resistant Staphylococcus aureus, which cause 25-30% of the cases in the published series; therefore, the results are not applicable to this population. On the other hand, the guidelines used, always with two drugs, are rather curious. There are serious doubts about the adequacy of the treatments used orally (see supplementary material), especially that of linezolid and rifampicin (by the way, administered at doses of 600mg/12 h) since there is evidence of their potential interaction after one week of coadministration. In an attempt to avoid this possible interaction, the levels of all the antibiotics administered orally were measured at day 1 and 5 after the beginning of the treatment to carry out further dosage adjustments. In 7 patients, the levels of antibiotics were infratherapeutic (rifampicin in 3 cases, moxifloxacin in 2, linezolid in 1 and dicloxacilin in another case). In my opinion, although the evidence offered in this study is strong compared to other studies, we must be cautious regarding the application of this therapeutic strategy in the daily clinical practice.

DOES PROCALCITONIN CHANGE THE WAY WE PRESCRIBE ANTIBIOTICS?

☞ ***Referencia Original:*** Huang DT, Yealy DM, Filbin MR, et al; ProACT Investigators. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. *N Engl J Med*. 2018; 379(3):236-249.

This is a randomised, multicentre clinical trial carried out in 14 hospital of the United States that includes patients over 18 years of age attended in ER for acute lower respiratory tract infection (<28 days), for whom their designated physician did not have a clear idea of the origin of the case and, therefore, whether or not it was necessary to prescribe antibiotics. These patients were randomised (1:1) into two groups: a) procalcitonin group (PCG), and b) usual management group (UMG), in which the physicians did not have the value of procalcitonin when establishing a clinical judgement and prescribing a treatment. Prior to the study, an important dissemination work about the interpretation of the values of procalcitonin was carried out in all the participating centres. In both groups, the responsible physician was completely free to decide which treatment was best to prescribe for the respiratory case. The primary objective of the study was the total use of antibiotics in both groups, measured as the total number of days of antibiotic use in the 30 days after inclusion. The study also included a safety primary objective to quantify the secondary effects related to the use of antibiotics at 30 days after inclusion in the study. Between November 2014 and May 2017, a total of 1664 patients were randomised (826 in PCG and 830 in UMG). In the intention-to-treat analysis, there were no differences in the number of days of antibiotic use between the two groups (mean: 4.2 in PCG and 4.3 in UMG; difference, –0.05 days; CI95% –0.6 to 0.5; p=0.87). Also, there were no significant differences in the presence of adverse effects related to the consumption of antibiotics in the two groups at 30 days (11.7% in PCG and 13.1% in UMG). In the analysis of the secondary objectives, there were no differences between PCG and UMG regarding the percentage of patients who received antibiotics in the 30 days after randomisation (57% and 61.8%, respectively; risk difference, –4.8 percentage points; IC99.86% –12.7 to 3.0), the percentage of patients who received antibiotics in the ER area (34.1% and 38.7%; risk difference, –4.6 percentage points; IC99.86% –12.2 to 3.0), or the average days of antibiotic use among the hospitalised patients (2.6 and 2.7 days; risk difference –0.1; CI99.86% –0.8 to 0.6).

COMMENT: Dr. Alberto Romero Palacios

This is an interesting article that approaches, from a different perspective, the usefulness of procalcitonin in the decision of whether to prescribe antibiotics. The accumulated literature about the use of procalcitonin as a diagnostic (and prognostic) marker of bacterial infections is solid and abundant. A good example of this is the recent meta-analysis published by Cochrane (*Cochrane Database Syst Rev* 2017;10:CD007498). However, the authors do not discuss the value of this analytical marker, but the influence it may have on the physician when prescribing antibiotics. Specifically, the question they

intend to answer with this study is: when procalcitonin is available, are there fewer antibiotics prescribed in ER for patients diagnosed with acute respiratory low tract infection? And, surprisingly, the answer is NO. Considering that the methodology of the study is quite solid and the results are consistent despite the multiple sub-analyses, there is an aspect that may limit the extrapolation of the results to our reality. This article shows that the hospitals selected to participate in the study have a high level of adherence to the recommendations of how to manage respiratory infections according to the *Joint Commission pneumonia core measures*, which greatly limit the prescription of antibiotics. Therefore, the room for improvement in these hospitals is narrow, regardless of the use of procalcitonin. This fact is in contrast to what we find in most ER rooms of Spanish hospitals, where there is an important healthcare burden on the physicians (of any specialty and mostly in the first years of residency), for whom the knowledge about the prescription of antibiotics is, at least, improvable. In this scope, from my point of view, any tool that allows resolving whether a respiratory infection is viral or bacterial will always be welcome. With this said, I consider that its use must be regulated, to ensure that it does not become merely one more analytical test in the set of usual analytical tests in the ER area.

NEUROLOGICAL SYMPTOMS IN PATIENTS WITH SYPHILIS. DO THEY PREDICT NEUROSYPHILIS?

☞ ***Referencia Original:*** Davis AP, Stern J, Tantalo L, et al. How Well Do Neurologic Symptoms Identify Individuals With Neurosyphilis? *Clin Infect Dis* 2018; 66:363-367.

Monocentric, observational study of a prospective cohort conducted in a hospital of Seattle (USA), between the years 1996 and 2014, which included HIV positive and HIV negative patients with serological diagnosis of syphilis and under risk of affectation of the central nervous system, either due to neurological symptoms or signs, RPR higher or equal to 1/32, or CD4 cell count below 350 cel/µL (in the case of HIV positive patients). None of them had a history of syphilis or previous treatment for such infection. All participants had lumbar puncture and VDRL test of the cerebrospinal fluid (CSF). The aim of the study was to analyse whether any specific symptom was associated with neurosyphilis, defined as VDRL positive in CSF. A total of 466 patients were included, 385 of which were HIV positive (99.5% males) with an average age of 39 years. Early syphilis was more frequent in HIV patients (69 vs 42%, p<0.001) with similar mean values of RPR in both groups (1/64). The VDRL test was positive in the CSF in 24.7% of the patients without HIV and in 17% of those with HIV, although without significant differences. Almost all patients had some neurological symptom, such as hypoesthesia (8.8 vs 3.7%) or loss of hearing (30.3 vs 17.2%), with greater clinical expressivity in HIV negative patients. In patients without HIV the association between neurosyphilis and neurological symptoms was not greater. However, there was a difference in RPR, with a greater ratio in patients with syphilis (1/128 vs 1/16, p<0.001). In HIV positive patients, some neurological symptoms were associated with neurosyphilis, such as photophobia [OR 2.0 (1.1-3.8)], loss of visual acuity [OR 2.3 (1.3-4.1)] and uncoordinated movement [OR 2.4 (1.3-4.4)]. As in the population without HIV, RPR was greater in those patients diagnosed with neurosyphilis (1/256 vs 1/64, p<0.001). There was no relation between the neurological manifestations and the CD4 cell count or viral load.

COMMENT: Dra. Isabel Antequera
Area Specialist Physician in Internal Medicine. San Agustín de Linares Hospital.

This study leaves more questions than answers. Although it has a prospective methodology, it was conducted for many years (almost 20) and includes two different populations (HIV negative and HIV positive patients), with unclear inclusion criteria that seem to have changed over time. The population with HIV has also changed in the last two decades, with different percentages regarding the use of ARV treatment and virological suppression. Moreover, for the diagnosis of neurosyphilis, only the VDRL test in CSF was used, which is a very specific test, but it has a very low sensitivity (below 50%).
What is the contribution of this study? The presence of some neurological symptoms in HIV patients predicts a positive VDRL test in CSF, which does not occur in the HIV negative population. Furthermore, the absence of neurological symptoms does not predict a negative VDRL in CSF and this occurs in both HIV positive and HIV negative populations.
To sum up, we must maintain the criterion of performing a lumbar puncture in patients with syphilis who have neurological symptoms. The diagnosis of neurosyphilis may be simple if the VDRL test is positive (most infrequently); however, if the VDRL is negative, in the absence of a more sensitive and specific test, the characteristics of the CSF will help us make a decision on whether or not we should proceed with the treatment.

IS THERE TANGIBLE EVIDENCE OF THE ASSOCIATION BETWEEN ZIKA VIRUS INFECTION AND MICROCEPHALY?

☞ ***Referencia Original:*** de Araújo TVB Ximenes RAA, Miranda-Filho DB, Souza WV et al. Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study. *Lancet Infect Dis 2018* (3) 18: 328 – 336.

This is a prospective study that analysed neonates born between January 15th and November 30th of 2016 from the health care zone of Pernambuco (Brazil), with a total of 91 cases and 173 controls. The study included those neonates with microcephaly (born alive or dead) whose head circumference was at least 2 SD below average for their sex and gestational age in the Fenton's growth chart. The exclusion criteria were: anencephaly, encephalocele and confirmation of the phenotype of a well-defined congenital syndrome. The controls were alive neonates without microcephaly, without brain abnormalities (determined by transfontanel ultrasonography) and without major congenital defects. The serum samples of mothers and neonates (cases and controls) and CSF samples (cases) were analysed by qRT-PCR for the detection of the genome of Zika and by IgM-capture ELISA. In 32 (35%) cases, the congenital Zika virus infection was confirmed through laboratory tests and no control had any confirmation of Zika virus infection. Sixty-nine (83%) out of 83 cases with known weight at birth were small for their gestational age, compared to eight (5%) out of 173 controls. The ratio for this global combined probability was 73.1 (IC95%, 13.0-∞) for microcephaly and Zika virus infection after adjustments. Neither vaccination during pregnancy nor the use of the larvicide pyriproxyfen were associated with microcephaly. The results of the laboratory tests for Zika virus and the results of the brain images were available for 79 (87%) cases, of which 10 were positive for Zika virus and had brain abnormalities, 13 were positive for Zika infection without brain abnormalities, and 11 were negative for Zika virus and had brain abnormalities.

COMMENT: Dr. Marcos Guzman

The causal link between Zika virus and microcephaly, as part of the congenital syndrome of Zika virus, is well-established in the present day; however, there was no confirmatory study with cases and controls. In this sense, the association between microcephaly and congenital Zika virus infection is confirmed, with this study being the largest carried out to date, although it has some aspects that deserve criticism. The authors provide evidence of the absence of an effect of other potential factors, such as exposure to pyriproxyfen or vaccines (tetanus, diphtheria and acellular pertussis, measles and rubella, or measles, mumps and rubella) during pregnancy. In a first read, it can be observed that the study has several limitations, such as the time of infection by the mother, since there are differences between the use of serology and PCR for Zika to confirm the contact of the mother, and also the sensitivity of the imaging tests for the determination of structural diseases. These limitations are mainly factors related to the lack of university protocols of action for this emerging phenomenon. There are also confounding factors, with the most important being the habit of smoking, followed by socio-economic factors. Lastly, and despite these factors, this study provides clear evidence of the strong association with Zika virus and, for the first time, it investigates other possible risk factors, which makes it the reality of the beginning of an emerging problem.

TEACHING, ON A LARGE SCALE, BETTER ANTIBIOTIC MANAGEMENT. ANOTHER GOOD INITIATIVE.

☞ ***Referencia Original:*** Pérez-Moreno MA, Peñalva-Moreno G, Praena J, et al. Evaluation of the impact of a nationwide massive online open course on the appropriate use of antimicrobials. *J Antimicrob Chemother* 2018; 73(8):2231-2235.

This study shows the results of the evaluation of an online course designed to improve the knowledge about the proper use of antimicrobials (AMC) employed in the main syndromes of infectious diseases. It was carried out at the national level in Spain in 4 months, was targeted to physicians and hospital pharmacists and was free-access. The authors designed a survey of 30 questions with quantifiable answers to be filled before and after the course. A qualitative evaluation of the activity was also conducted. A total of 2,148 professionals offered to participate. The survey was completed before and after the course by 606 participants, 81.2% physicians and 15.4% pharmacists. Combined, the mean score before and after the course was 6.2 + 1.38 and 7.9 + 0.88, respectively (increment of 1.8 + 1.21, P<0.001). The qualitative evaluation of the activity was very positive. Specific areas with remarkable improvement of their knowledge were the criteria to measure the plasma levels of vancomycin, the antifungal treatment of post-chemotherapy febrile neutropenia, the treatment of febrile neutropenia in patients with lung cancer, the treatment of candidemia and of infections caused by extended-spectrum betalactamase-producing enterobacteriaceae and the application of the criteria for the empirical treatment of pneumonia associated with air conditioning units.

COMMENT: Dr. Manuel Torres Tortosa

It is a fact that any clinical specialist can prescribe AMC to their patients and this does not seem to be changing in the future. On the other hand, the use of AMC, besides the therapeutic action in a specific patient, has a great ecological impact, especially in hospitals, where many patients receive AMC, and this creates an environment with patients, professionals and medical equipment in close contact. Therefore, initiatives like the one commented here are important for the expansion of

the proper use of AMC, especially in severe clinical situations that lead to high mortality. This does not prevent the direct involvement of infectologists in the management of these patients in close collaboration with the rest of the professionals involved.

WHAT IS THE BEST TREATMENT FOR CLOSTRIDIUM DIFFICILE INFECTION, ACCORDING TO THE MOST EXTENSIVE NETWORK META-ANALYSIS?

☞ ***Referencia Original:*** Tumas Beinortas, Nicholas E Burr, Mark H Wilcox, et al. Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis. *Lancet Infect Dis* 2018;18:1035–44.

Clostridium difficile infection is a growing issue against which new drugs have been developed. The study commented here, a comparative network meta-analysis about the efficacy of the different therapeutic alternatives available against *C. difficile* infection, will help us to better understand the current state of the treatment for this pathology. Therapies based on monoclonal antibodies were not included. The authors conducted an extensive network meta-analysis which, after a thorough selection, included 24 clinical trials, with a total of 5,361 patients and 13 different treatments. The main *end-point* was the sustained symptomatic recovery, that is, the resolution of diarrhea, discarding remissions and deaths. The summary of the results with their odds ratios was the following: (1) fidaxomicin 0.67 and teicoplanin 0.37 obtained significantly better results than vancomycin; (2) teicoplanin 0.27, ridinilazole 0.41, fidaxomicin 0.49, surotomycin 0.66 and vancomycin 0.73 showed better results than metronidazole; (3) bacitracin was inferior to teicoplanin 0.22 and fidaxomicin 0.40; (4) tolevamer was inferior to all except LFF571 0.50 and bacitracin 0.67. Metronidazole has been widely recommended as a first-line treatment in initial, mild and moderate infections. In 2018, the recommendations of the *European Society of Clinical Microbiology and Infectious Diseases* were modified, with oral vancomycin and fidaxomicin becoming the drugs of choice and metronidazol being consigned to the treatment of mild/moderate infections in those cases in which the access to vancomycin or fidaxomicin is limited. Afthe this meta-analysis, a further step is made. The authors consider fidaxomicin the drug of choice. However, in the most severe cases, the recommendation is still vancomycin, since this is the rigorous scope of meta-analysis, where the number of existing studies supporting the recommendation is important. The authors discredit the use of metronidazol, both orally and intravenously. Oral teicoplanin proved to be an efficient drug, perhaps the second best drug after fidaxomicin; however, the scarce number of studies supporting it does not allow a wider recommendation.

COMMENT: Dr. Jesús Canueto

We find in an important journal the study that proposes all the ideal conditions to answer, in a definitive manner, a question that has a considerable clinical interest: should we treat septic shock patients with corticoids? The expert guide books recommend so, but they state that the evidence supporting this recommendation is weak. Nothing like a pragmatic, randomised, double-blind, multi-centre and international clinical trial to answer to this question? The answer, in view of the results, is that the use of corticoids does not decrease mortality neither at 90 days nor at 28 days in these patients. However, and following the criteria of a critical reading, I wonder if this is the ultimate study that will change the clinical practice in this field. And I rather think not. I think that the mortality rates at 90 days presented in this study (27.9% in the corticoid group and 28.8% in the placebo group) are lower than the mortality rates at 90 days that the authors estimated when they calculated the sample size (33%), which, inevitably, affects the strength of the study, which initially aimed to show differences of 5% or above between the two groups. Thus, the remaining doubt is whether they would have found significant differences with a larger sample size or with a mortality rate similar to the one initially estimated. Another aspect that is worth highlighting is the discordance between the results obtained in the main objective and some of the secondary objectives. Whereas, the main objective does not show differences in mortality at 90 days between the use or not of corticoids in septic patients, in the following secondary objectives the results were significantly in favour of the use of corticoids: shorter time until recovery from the shock, shorter time until discharge from the ICU and shorter duration of the initial ventilation episode. And the discussion section of the article does not shed much light over this discordance, other than the hypothesis that they might show a beneficial hemodynamic effect of hydrocortisone. With respect to the also significantly lower need for blood transfusions in the corticoid group, they do not provide any hypothesis. From my point of view, although the evidence offered by this study is undoubtedly more solid than the evidence provided in the literature so far, the defenders of the use of corticoids in severe sepsis can find arguments to refute the results of this study if they want to keep their intention to use them.

NEWS

• Coinciding with the 10th anniversary of the founding of the GAMES group, on **November 16th and 17th**, the **National Congress of the Spanish Society of Cardiovascular Infections (SEICAV)** will be held in Seville. For more information: http://www.seicav2018.com.

• AID is open to everyone who enjoy and has interest in infectious diseases. To make a collaboration with the journal write to Dr. Eduardo López Cortés (luiselopezcortes@gmail.com).

• We remind that the section "Clinical Images" is open. For publish an image on SAEI´s website and in AID, send an e-mail to Dr. Ángel Domínguez (adomin60@gmail.com) with a short clinical summary.

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