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EDITOR´S CHOICE

PREVENTION OF TUBERCULOSIS-ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME: PREDNISONE, WHO ELSE?

☞ ***Referencia Original:*** G. Meintjes, C. Stek, L. Blumenthal, F. Thienemann, et al for the PredART Trial Team. Prednisone for the Prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med* 2018;379:1915-25.

A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of prednisone to reduce the incidence of tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) in patients at high risk for the syndrome. The study was conducted at a HIV-TB clinic in Cape Town, South Africa. A total of 240 HIV-infected patients who where initiating antiretroviral therapy, ART (and had not previously received ART), had started tuberculosis treatment within 30 days before initiating ART, and had a CD4 count of 100 cells of fewer per microliter (median 49 CD4 cells, IQR 24-86) were enrolled. 73% had microbiologically confirmed tuberculosis. Tuberculosis treatment consisted of the standard for the intensive-phase (rifampin, isoniazid, pyrazinamide, and ethambutol) and the ART regimen was tenofovir, emtricitabine (or lamivudine), and efavirenz for 97.1% of the patients. A total of 120 patients were assigned to each group. Patients received either prednisone (at a dose of 40 mg per day for 14 days, then 20 mg per day for 14 days) or placebo. Treatment with prednisone or placebo started within 48 hours after the initiation of ART. Follow-up visits where scheduled until week 12, with an additional visit at week 28 and a phone call at 1 year to monitor for HIV-related cancers. Tuberculosis-associated IRIS was diagnosed in 39 patients (32.5%) in the prednisone group and in 56 (46.7%) in the placebo group, relative risk 0.70 (95% CI: 0.51-0.96, p=0.03). Secondary efficacy and safety end points: Open-label glucocorticoids were prescribed to treat more severe tuberculosis-associated IRIS in 16 patients (13.3%) in the prednisone group and in 34 (28.3%) in the placebo group, RR 0.47 (95% CI: 0.27-0.81). There were 5 deaths and severe infections (acquired immunodeficiency syndrome-defining illnesses or invasive bacterial infections) occurred in 11 patients in the prednisone group and there were 4 deaths and 18 patients with severe infections in the placebo group (p=1.00 y p=0.23, respectively). One case of Kaposi's sarcoma occurred in the placebo group. There was no significant difference between the groups in CD4 cell count or HIV-1 RNA suppression at week 12.

COMMENT: Dra. Ana Belén Lozano
Hospital de Poniente. GEPISI.

Tuberculosis is the most common opportunistic infection in HIV-infected patients. Tuberculosis-associated IRIS is an immunopathologic reaction characterized by worsening or new inflammatory features of tuberculosis that manifest in patients initiating ART. It usually occurs in the first 4 weeks after ART initiation in 4-54% of the patients, causes a considerable morbidity that requires hospitalization in 25% of the cases and has an attributable mortality of 2%. Low CD4 counts and a short interval between the start of antituberculosis treatment and the start of ART increase the risk of tuberculosis-associated IRIS. However, early initiation of ART in patients with low CD4 counts is associated with a higher survival rate and thus, for those with < 50 CD4/ µL, rapid ART initiation within 2 weeks after antituberculosis-treatment start is recommended. Until the release of this clinical trial and its preceding presentation at CROI 2017, no evidence-based strategy to prevent tuberculosis-associated IRIS existed. This study proves that prophylactic prednisone during the first 4 weeks after the initiation of ART in adult patients with low CD4 counts can safely (without evidence of an increased risk of severe infections or cancers or other adverse effects) reduce by 30% the incidence of tuberculosis-associated IRIS. The possibility of hypothalamic-pituitary-adrenal axis suppression is not mentioned among prespecified adverse events related to glucocorticoid treatment (Supplementary appendix, table S 19) although such suppression is likely when daily doses of at least 20 mg of prednisone for more than 3 weeks are used (Furst DE, Saag, KG. Glucocorticoid withdrawal. This topic last updated: Jul 12, 2017. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2018). Whatsoever, prednisone plasma concentrations reached in the study population might be lower due to interactions with rifampin, which increases prednisone clearance by 45%, reducing its bioavailability. After the communication of the results of this study at CROI 2017, the indication for the prophylactic use of prednisone in people with tuberculosis starting ART with less than 100 CD4 /µL was settled in the last version of the national Spanish GESIDA guidelines (Documento de consenso de GeSIDA/PNS sobre TAR, enero 2018).

GUEST COLLABORATOR

DOSAGE ERRORS WITH CEFTOLOZANE/TAZOBACTAM (ZERBAXA®): ARE WE MISINTERPRETING THE GUIDELINES?

☞ ***Referencia Original:*** 1. FDA Drug Safety Communication: FDA cautions about dose confusion and medication errors for antibacterial drug Zerbaxa® (ceftolozane and tazobactam). United States Food and Drug Administration. FDA. [Internet].
2. Mensa J., Gatell J.M. et al. Guía de Terapéutica Antimicrobiana 2017. Barcelona: Editorial Antares; 2017.

COMMENT: Dra. María Núñez-Núñez (UGC Farmacia. Hospital Universitario San Cecilio Granada), Pelayo Nieto (UGC Enfermedades Infecciosas. Hospital Universitario San Cecilio Granada), Francisco Anguita (UGC Farmacia. Hospital Universitario San Cecilio Granada)

Ceftolozane/tazobactam (C/T) is an antibiotic recently commercialised as a combination of a new cephalosporin, structurally similar to ceftazidime, with fixed doses of tazobactam as a beta-lactamase inhibitor. It is active against broad spectrum β-lactamase producing enterobacteriaceae and multidrug-resistant (MDR) *Pseudomonas aeruginosa*. C/T has been authorised in adult patients for the treatment of complicated intraabdominal infections in combination with metronidazole, and complicated urinary tract infections (cUTIs), including pyelonephritis, with increasing evidence of use for other indications, such as pneumonia or bacteremia.Dosage and administration errors: Each vial of Zerbaxa® contains 1 g of ceftolozane and 0.5 g of tazobactam, with a usual dose of 1 vial every 8 hours, or double dose in cases of severe infection, including pneumonia. However, we are observing in hospitals that 50% more than the prescribed dose is frequently administered. In 2015, the Food and Drug Administration of the USA [1] approved a change in the labelling due to the high frequency of dosage errors and, therefore, the sum of the two active ingredients is currently indicated (doses of 1.5 g, equivalent to 1 g of ceftolozane and 0.5 g of tazobactam). Consequently, the reference guidelines recommend standard doses of 1.5 g and 3 g for severe infections. The opposite occurs in Spain: since the dose of the betalactamase inhibitor is fixed, the dosage in the systems of electronic prescription is usually established according to the individual doses of the betalactam, as is the case of piperacillin-tazobactam 4/0.5 g or amoxicillin-clavulanate 1/0.2 g, which are indicated as 4 g and 1 g, respectively. However, the Spanish guidelines, or those translated into Spanish, have maintained the doses expressed as the sum of the two active ingredients (1.5-3 g), inducing frequent administration errors. Some of these guidelines have been changed and/or indicate both options, as is the case of the Mensa's guidelines of antimicrobial therapies [3], which in its 2017 edition indicated "1.5-3 g (1-2 g of ceftolozane with 0.5-1 g of tazobactam)".We hope that our experience will be useful for other antibiotic-use-optimization teams to prescribe and audit prescriptions of this drug.

GUEST COLLABORATOR

EFFICACY AND SAFETY OF THE EARLY SEQUENTIAL TREATMENT IN *STAPHYLOCOCCUS AUREUS* BACTEREMIA.

☞ ***Referencia Original:*** Willekens R, Puig-Asensio M, Ruiz-Camps I, et al. Early oral switch to linezolid for low-risk patients with *Staphylococcus aureus* bloodstream infections: a propensity-matched cohort study. *Clin Infect Dis* 2018. En prensa.

This study compares two cohorts: the one composed of patients treated with oral linezolid from the third to the ninth day of treatment, and the one constituted by patients treated according to the standard recommendation, with parenteral treatment in all cases. The two cohorts were adjusted by pairing (1:2) the significant variables selected through *propensity score* to receive the sequential treatment. The authors compared the safety and efficacy of the two treatment guidelines, as well as the duration of the hospital stay. Only clinically stable patients were included, with negative control blood cultures and a good management of the source. The patients with complicated bacteremia, those who had an osteoarticular source and those who died before day 7 were excluded from the study. The cohorts included a total of 45 and 90 patients for oral linezolid and the standard recommendation, respectively. The authors did not find differences in the relapse percentage in the following 90 days (main *outcome*), nor in mortality at 30 days, whereas hospital stay was significantly lower in the group of early sequential treatment. Despite the observational nature of the study, these results are valuable in view of the absence of randomised clinical trials that evaluate this issue, although it is important to take into account some relevant aspects on which I reflect below.

COMMENT: Dr. Oriol Gasch
Department of Infectious Diseases. University Hospital Parc Taulí. Sabadell, Spain.

With respect to the composition of the two compared groups, despite the fact that there are only significant differences in the percentage of patients with chronic kidney failure (lower in the group of patients treated with linezolid), the cohort with the standard treatment had a greater proportion of patients in hemodialysis, alterations with a tendency to endocarditis, septic shock, unknown source and absence of interconsultation with the specialist. All this raises doubts about the comparability of the two groups, in spite of the pairing by the selected variables, which should have included endovascular devices, for example. Moreover, it would have been appropriate to know how many of the 44 patients excluded for dying before day 7 were on oral linezolid treatment at the time of death. Secondly, the design of the study is based on an assumption that must be reviewed: the definition of the cohort of patients who receive the standard treatment admits the use of any parenteral antibiotic to which the microorganism is sensitive (excluding aminoglycosides). With this definition of correct antibiotherapy, an important percentage of patients in this cohort received betalactam/betalactamase inhibitor, cefepime, teicoplanin or IV linezolid, which probably should not be considered as standard treatments, especially since the use of some of them have been associated with worse evolution in previous studies. I recommend reading the editorial 'What is inadequate antibacterial therapy?' by Dr RC Moellering Jr. (*Clin Infect Dis*. 2009; 49(7):1006-8). Regarding the sequential treatment selected, linezolid is an antibiotic with bacteriostatic activity against *S. aureus*, despite which its early oral use was not associated with worse clinical evolution. These results lead to three reflections. First, the inclusion and exclusion criteria of the study help delimit a population of patients with low-risk *S. aureus* bacteremia, in which the bactericide activity of the treatment is probably not so determining as in cases of complicated bacteremia or endocarditis. Secondly, it seems probable that other oral treatments, with or without bactericide activity against *S. aureus*, could obtain similar results in this population of patients. In any case, this speculation needs to be evaluated for each antibiotic. Thirdly, it is important to highlight that the conclusions of this study cannot be extrapolated to complicated bacteremia. Lastly, a reflection on the events of the main dependent variable: only five relapses were diagnosed in the two treatment groups (<4%). This datum can be read as an adequate selection of patients with low risk (high negative predictive value), eligible to be included in the study. However, it is surprising that only 36% and 56% of the participants of each cohort were subjected to transthorathic echocardiogram or transesophageal echocardiography, as part of the statification of the risk; moreover, there was up to 20% of bacteremia of unknown source, usually associated with worse evolution. Some authors consider that primary bacteremia caused by *S. aureus* without a known gateway, as well as those diagnosed in patients who bear intravascular devices, must be managed as complicated bacteremia in all cases. There is room for debate, since, once again, the available scientific evidence is not enough. The five relapse cases diagnosed allow speculating about the possibility of improving the selection of low-risk bacteremia, which are supposed to contribute to an early sequential treatment, with, for instance, a radioisotope analysis (in addition to the echocardiogram), thus increasing the capacity to detect septic embolism with respect to anamnesis, and physical exploration. Despite the doubts raised by the aspects commented above, the results of this study seem to indicate that the early sequential treatment with linezolid is effective and safe in this population of patients. Randomised studies are needed to expand the scientific evidence provided by observational studies.

GUEST COLLABORATOR

IS IT NECESSARY TO USE GENTAMICIN IN THE ANTIBIOTIC TREATMENT OF PATIENTS WITH STAPHYLOCCOCAL PROSTHETIC ENDOCARDITIS?

☞ ***Referencia Original:*** Ramos-Martínez A, Serrano AM, de Alarcón González A, et al. Gentamicin may have no effect on mortality of staphylococcal prosthetic valve endocarditis. *J Infect Chemother* 2018 Jul;24(7):555-562.

The authors of this study evaluated the role of gentamicin in the antibiotic treatment of patients with staphyloccocal prosthetic endocarditis. To this end, they conducted a retrospective analysis of the data from the SSGMIE cohort (Spanish Support Group for the Management of Infectious Endocarditis), gathered between the years 2008 and 2016 from 27 Spanish hospitals. The study included a total of 94 cases of staphyloccocal prosthetic valve endocarditis treated with a regime based on either vancomycin or cloxacillin. This treatment included rifampicin in all cases, and gentamicin in 82% of the patients. The causative germ was coagulase-negative *Staphylococcus* in 57.5% and *Staphylococcus aureus* in 42%. The clinical characteristics and the mortality were compared according to the administration of gentamicin. There were no statistically significant differences in the clinical characteristics, in the presence of complications or in the surgery rates between the two groups. Mortality during admission and after one year of treatment was also similar (42.9% vs 41.2%, p 0.89; 49.4% vs 47.1%, p 0.86). The variables that were independently associated with a worse prognosis were the presence of heart failure (OR 4.58) and the absence of surgery despite this being indicated (OR 2.68). The association or no association of gentami-

cin was not related to mortality, although it was neither significantly related to worse kidney function. The authors concluded that the addition of gentamicin was not associated with better clinical results in these patients.

COMMENT: Dr. Guillermo Ojeda Burgos
Department of Infectious Diseases. University Hospital Virgen de la Victoria, Málaga, Spain. Study group GEICAV.

The present work leads to questioning the risk-benefit ratio of including gentamicin in the treatment of staphyloccocal prosthetic endocarditis. It is a question that raises frequently in the clinical practice, since staphyloccoci are the main germs involved in this type of endocarditis, and the addition of gentamicin to a regime based on rifampicin and cloxacillin or vancomycin is a synergistic combination that is well-established in the main clinical guidelines. On the other hand, the population that suffers from this type of endocarditis is increasingly older, multipathological and multimedicated, and thus more susceptible to suffer the adverse effect of this antibiotic. Therefore, the conclusion drawn by the authors is very attractive from the clinical perspective, since it reinforces the decision of not adding gentamicin in complex cases such as the ones mentioned.
However, this study shows some considerations that limit the applicability of its results, with the most important being the low number of patients included in the group that did not receive gentamicin. Moreover, the results mix patients with infections caused by coagulase-negative *Staphylococcus* and *S. aureus*, with a lower number of the latter, thus the conclusions show mostly infections caused by less aggressive germs. The regimes compared are also different, with up to four different combinations of antibiotics possible. Lastly, many of the included patients had several comorbidities, with basal kidney failure in 25%. These aspects limit the generalization of the results to a subgroup of patients with low representation in this study, such as younger patients with few comorbidities. In conclusion, this study poses one more step in the search for safer regimes for our patients, with results that support the decision of not using gentamicin in patients with staphyloccocal prosthetic endocarditis who, due to their comorbidities, show a high risk of toxicity associated with this antibiotic. Although no conclusive information is provided for decision-making, especially in the case of infections caused by *Staphylococcus aureus* and in the younger population, this study paves the road for the revision of the triple therapy in these infections, in which obtaining evidence from clinical trials is difficult.

GUEST RESIDENT

VAGINAL TRICHOMONIASIS. IS A SINGLE DOSE OF METRONIDAZOLE ENOUGH TO TREAT IT?

☞ ***Referencia Original:*** Kissinger P, Muzny CA, Mena LA, et al. Single-dose versus 7-day-dose metronidazole for the treatment of trichomoniasis in women: an open-label, randomised controlled trial. *Lancet Infect Dis* 2018; 18(11):1251-1259.

This was a multi-centre clinical trial carried out in the United States between October 2014 and April 2017. It included an initial sample of 1028 women, of whom only 623 were registered, as a result of the early termination of the study due to funding problems. Most of the participants were Afro-American, with an average age of 27 years, and diagnosed with an infection by *Trichomonas vaginalis* without concomitant HIV infection. They were randomly distributed (1:1) into two treatment groups: a) current standard treatment with a single dose of 2 g of metronidazole, and b) administration of 500 mg of metronidazole every 12 hours for 7 days. The diagnosis of infection by *Trichomona Vaginalis* was conducted through nucleic acid amplification test (NAAT), Gram stain and culture, whereas the diagnosis of bacterial vaginosis was clinical (score higher or equal to 7 Nugent criteria). The main objective of the study was to evaluate the efficacy of the two guidelines with respect to the eradication of *Trichomona Vaginalis* at four weeks after the termination of the treatment, as well as the role of the status of bacterial vaginosis (present in 294 participants) in such efficacy. The proportion of women in whom a negative result was obtained in the detection of *Trichomona vaginalis* was greater in the treatment group with 7-day metronidazole (34/312; 11%) than in the single-dose group (58/312; 19%), with a RR of 0.55 (CI 95% 0.34-0.7; $p < 0.0001$). The presence of bacterial vaginosis did not have a significant effect on the result (p=0.17). Other parameters analysed were: 1) self-informed adherence to treatment (96% in the 7-day metronidazole group and 99% in the single-dose group with p=0.006), and 2) secondary effects derived from the use of metrodinazole, with nausea as the most common one (23%), followed by cephalea (235) and vomiting (4%). In view of the observed results, the authors of this study concluded that the best treatment for trichomoniasis in a woman without HIV infection is 500 mg of metronidazole every 12 h for 7 days.

COMMENT: Dra. Rosario Castilla Ortiz
Fourth-year resident in Internal Medicine. University Hospital Puerto Real, Cádiz, Spain.

Trichomoniasis is the most frequent non-viral sexually transmitted infection and it is associated with high reproductive and perinatal morbidity, hence the importance of this study. Its results suggest that the current standard treatment could be in-

sufficient. This standard guideline derives from the evidence produced in very old studies in which the analysed population were women with HIV infection. In them, it was demonstrated that the treatment with metronidazole for 7 days was more efficient than the single-dose treatment, but only when it coexisted with bacterial vaginosis. Therefore, the use of the weekly treatment for isolated trichomoniasis was not generalized to the whole population. However, we are currently beginning to know that patients with HIV infection can show an alteration of their microbiota, and that this could have behaved as a confounding factor when analysing the results from previous studies. Therefore, it can be asserted that this study provides solid evidence to contemplate a change in the paradigm for the treatment of trichomoniasis that has been considered to date, recommending from now on the guideline of metronidazole 500mg/12 hours for 7 days without the coexistence or no coexistence with bacterial vaginosis modifying this attitude in any way.

THE CURRENT REFUSAL TO PROVIDE TREATMENT AGAINST HEPATITIS C IN THE USA: AN UNPRECEDENTED SCANDAL, ESPECIALLY FROM THE ETHICAL PERSPECTIVE.

☞ ***Referencia Original:*** Ch Gowda, S Lott, M Grigorian et al. Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study. *Open Forum Infect Dis* 2018; 5(6):ofy076.

This is a prospective cohort study conducted in the USA that evaluates the absolute refusal to provide hepatitis C treatment (HCVT) with direct-acting antivirals (DAA), despite having medical prescription, globally and depending on the type of insurance company (Medicaid, Medicare and commercial) from January 2016 to April 2017. Among 9,025 patients from 45 states evaluated during the study period, HCVT was denied to 3,200 (35.5%). This refusal was more frequent with commercial insurance companies (52.4%), compared to Medicaid (34.5%; p<0.001) and Medicare (14.7 %, p<0.001). The incidence of absolute negation to provide HCVT increased throughout the four quadrimesters of the study period (from 27.7% to 43.8%, p<0.001) and for all types of insurance company.

COMMENT: Dr. Manuel Torres Tortosa

HCVT with DAA has caused a unique paradox: on the one hand, it produced one of the most extraordinary achievements in antimicrobial therapy, as it achieved a recovery rate of practically all the patients who were treated with an easily administered treatment; on the other hand, this treatment has been commercialised by the involved companies with very high and clearly excessive prices. As a consequence, the results of this study pose an unprecedented scandal, especially considering that hepatitis C is a highly prevalent disease with severe morbimortality in the long-term. It is worth highlighting that the price of sofosbuvir (50,000 to 100,000 €) was recently one thousand times higher than its production cost (50 a 100 €) per treatment [1]. Apparently, this continues to occur in some scopes for the benefit of companies and to the detriment of the health of millions of people. It is also surprising that, in this day and age, citizens stoically and obediently accept such atrocities, when we should expect, considering the current social response until recently, a powerful protest mobilization to end this clearly abusive situation, with healthcare professionals, especially doctors, leading this protest. In 1948, Nye Bevan, founder of the National Health Service said "*No society can legitimately call itself civilized if a sick person is denied medical aid because of a lack of means*". And now, 70 years later, we are so far from that. Where are we heading? Why do we consent this?

MIGRANTS IN THE MEDITERRANEAN. DO THEY POSE A HEALTH DANGER?

☞ ***Referencia Original:*** Ciccozzi M, Cella E, Ceccarelli G, et al. Sentinel surveillance data from Eritrean migrants in Italy: The theory of "Healthy Migrants". *Travel Med Infect Dis*. 2018; 22:58-65.

This study is focused on the population of Eritrea (a country of limited health resources, with the largest number of migrants to die in the Mediterranean this year) that reaches the coast of Italy in the migratory current. The authors evaluated the concept of healthy migration, with special emphasis on the change in the initially healthy state of this population from a very deteriorated geographical area, which, usually after a variable period of time in the destination area, deteriorates for reasons that are still to be determined. The study included 133 Eritreans who arrived in Italy in a specific period of time of 2016 in three groups; they were given a general check-up, with special attention to transmissible infectious diseases: serological determination of HBV, HCV and HIV, and colonization test (similar to that conducted in hospitals: rectal, pharyngeal, axillar and inguinal). The control group consisted of 25 workers of the Asylum Application Centre where the migrants stayed after their arrival. The migrants were 70% males, with an average age of 22-23 years, whereas the workers were 48% males, with an average age of 36 years. The serological tests conducted were HCV negative in all cases and HBV with an expected prevalence. One case of HIV was diagnosed. The isolates of the colonization tests showed that in the Eritrean migrants there was a variable frequency of GNB, mainly *K. pneumoniae* and *K. oxytoca*, and *E coli* BLEE in 25%. The GP isolates were mostly *S. pneumoniae*, *S. pyogenes* and *S. dysgalactie*, and *S. aureus*. It is worth highlighting the frequency of polymicrobial isolates, which were in 32-44%. There was an isolate of *C. albicans* and uncommon microorganisms in few samples.

Among the workers of the centre, the percentages of GN isolates (*K oxytoca*, *Pseudomonas spp* and *Citrobacter*) and GP isolates (*Staphylococcus spp*) were lower than those of the migrants, and the polymicrobial test was negative in all cases. The authors concluded with the need to provide a systematised health evaluation to the migrant population, given that there are neither standardised protocols nor reliable registries to compare and make decisions. The absence of similar flora in the workers of the centre demonstrates that there is no risk of transmission, especially regarding resistant microorganisms. Knowing the colonisers in this population allows improving healthcare assistance, either by the higher presence of unusual microorganisms in our environment or by the higher presence of resistance to antimicrobials and the possible subsequent problems, especially knowing that, in many cases, health deteriorates after a period of time in the host country. Furthermore, the results of this study disagree with the stigma that associates possible transmissible diseases with migrants.

COMMENT: Dr. Leopoldo Muñoz Medina

Department of Infectious Diseases. University Hospital San Cecilio. Granada. GEPISI research group.

This study reflects on several healthcare aspects:
1.- The dramatic situation in the Mediterranean suffered by migrants who come from very disadvantaged countries with a practically inexistent healthcare system.
2.- The need to systematise a complete, respectable and consensual health evaluation, with the aim of improving the conditions of such migrants once in European soil.
3.- The differences regarding the present colonization in migrants compared to natives of the host country, and the possible influence of this on the health of migrants.
4.- The absence of microbial contamination in the staff who work directly with these migrants, thus demystifying the belief that migrants transmit diseases and pose a danger.
In any case, articles like this are necessary to show the current humanitarian problem there is in the Mediterranean and the need to provide not only social and political coverage, but also healthcare coverage, for a better assistance in the host country. If it can make us reflect once more, in this case from the epidemiological perspective, on the differences between more or less developed countries, may it be welcome.

THE TETRAVALENT DENGUE VACCINE IN CHILDREN: IS IT EFFECTIVE? ...AND REALLY SAFE?

☞ ***Referencia Original:*** Sridhar S, Luedtke A, Langevin E, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med*. 2018; 379(4):327-340.

There is a controversy regarding the efficacy and safety results of a tetravalent dengue vaccine (CYD-TDV), especially in children. In the trials used to evaluate its efficacy, excessive hospital stays due to dengue were observed, especially among vaccine receivers between 2 and 5 years of age, which was the reason why the administration of vaccines was not assumable, since the safety of its implementation was unknown. Then, this study was developed, which analysed vaccination in several age groups in children. Such investigation was based on a study of control cases with direct specific follow-up. The authors associated the changes related to an immunosorbent linked to anti-non-structural dengue 1(NS1) IgG enzymes as an immunological marker and used samples from month 13 to infer the serological status for a post-hoc safety and efficacy analysis. For the main analyses, the authors used the basal serological status determined from the results of a 50% plaque reduction neutralization test (PRNT50). The risk of hospitalization for virologically confirmed dengue (VCD), of severe VCD and symptomatic VCD according to the serological status of the dengue case, was estimated by means of weighted Cox regression. The cohort of cases included the 3,578 participants in the subcohort (2,384 in the vaccine group and 1,194 in the control group), as well as all the participants of the trials who had symptomatic VCD (1258 cases), hospitalization for VCD (644 cases), or severe VCD (142 cases). Among the seronegative dengue patients between 2 and 16 years of age, the cumulative incidence of hospitalization at 5 years was 3.06% in those vaccinated and 1.87% in the control group (hazard ratio (HR) vaccine vs control: 1.75; confidence interval [CI95%1,14-2.70). Among the seronegative dengue patients between 9 and 16 years of age, the cumulative incidence of hospitalization for VCD was 1.57% among those vaccinated and 1.09% among the control patients (HR 1.41; CI95% 0.74-2.68). Similar tendencies toward an increased risk were found with more frequency among the receivers of seronegative vaccines with respect to the seronegative controls for severe VCD. Among the seropositive dengue participants between 2 and 16 years of age and between 9 and 16 years, the cumulative incidence of hospitalization for VCD was 0.75% and 0.38%, respectively, among those who received the vaccine and 2.47% and 1.88% among the control participants, with HR 0.32 (CI 95% 0.23-0.45) and 0.21 (CI95% 0.14-0.31). The risk of severe VCD was also lower among the receivers of seropositive vaccines compared to the seropositive controls. It was concluded that CYD-TDV protected the receivers against severe VCD and prevented hospitalization for VCD for 5 years in people who had been exposed to dengue before vaccination; in addition to this, there was evidence of a higher risk in vaccinated people who had not been exposed to dengue.

COMMENT: Dr. Marcos Guzmán

The aim of this study was to determine efficacy ranges in order to endorse the safety and efficacy of CYD-TDV according to the serological status of dengue at the time of vaccination; the study is also aimed to influence the implementation of vaccination programs against dengue, taking into account the economic and social aspects related to the generalised commercialization of the vaccine. The information provided in this study is abundant but difficult to interpret, since the immunopathological mechanisms related to the infection and immunity linked to dengue are unknown. Among the most relevant data, the rates of hospitalization for VCD and severe VCD were higher in the vaccine group than in the control group in the seronegative cohort. There was also a tendency toward a higher risk of hospitalization for VCD associated with vaccination among the seronegative participants between 9 and 16 years of age. The findings indicate that previous exposure to dengue have a significant influence on the efficacy of the vaccine and provide some evidence of the possible effect of age. However, since age is associated with exposure to dengue, it is not clear whether these findings reflect an undetected exposure to dengue. All this suggests that the vaccine protects those who had been previously exposed, but it increases the risk of hospitalization and severe diseases among those who have never been exposed. Therefore, these numbers must be interpreted with caution, since they reflect the epidemiological contexts of the clinical trials, and they are expected to be different in real life. And this raises a question: should we assume that the more global approach, which involves massive vaccination campaigns, is the best way to save as many lives as possible, accepting the risk in healthy patients? We still need further results to answer this question.

ANTI-CLOTTING OF *S. AUREUS* THROMBOPHLEBITIS. STILL NO EVIDENCE TO DATE.

☞ ***Referencia Original:*** Wilson Dib R, Chaftari AM, Hachem RY, et al. Catheter-Related *Staphylococcus aureus* Bacteremia and Septic Thrombosis: The Role of Anticoagulation Therapy and Duration of Intravenous Antibiotic Therapy. *Open Forum Infect Dis* 2018; 5(10):ofy249.

This is a retrospective, observational study carried out between 2005 and 2016 in the MD Anderson cancer hospital of Texas. The cohort consisted of patients with *S. aureus* bacteremia related to catheter, who had a radiological diagnosis of septic thrombophlebitis. The main variable was composite, and it included the following: (1) persistence of fever after 7 days of adequate antibiotherapy, (2) persistence of the bacteremia in the described conditions, (3) relapse in the following 3 months, development of a complication related to the bacteremia (septic arthritis, soft-tissue abscess, meningitis, osteomyelitis or lung embolism), (4) crude death rate in the following 3 months. A total of 128 patients met the inclusion criteria, with an average age of 55 years; 62% of them had hematologic neoplasia (23% neutropenic upon diagnosis of the bacteremia). Forty-seven percent of the cases were caused by MRSA. Only 55% of the patients showed clear evidence of thrombophlebitis. With respect to the clinical handling, 94% of the catheters were removed in the diagnosis. The antibiotherapy was varied (vancomycin 84%, daptomycin 47%, cefepime 32%, linezolid 25%), and it is worth highlighting that only 38% of the MRSA were treated with cloxacillin. The average duration was 30 days (range: 3-161), with a median of 24 days of intravenous treatment (range: 1-69). It was decided to anti-clot (at the discretion of the physician) 69% of the cohort (average duration of 91 days, range: 1-500), with higher frequency in the cases of deep thrombosis; p=0.013). Interestingly, lung embolism was more frequent in the cases of superficial thrombosis (25% vs 6%, p=0.01). The patients whose intravenous treatment duration was between 14 and 27 days showed greater mortality with respect to those who received at least 28 days (31% vs 5%, p=0.001); this finding was confirmed in a multivariate analysis that is not shown in the article. The authors concluded that it is necessary to maintain treatment IV for at least 4 weeks, and to anti-clot those patients who suffer from *S. aureus* thrombophlebitis.

COMMENT: Dr. Luis Eduardo López Cortés

There are few published data about the need to anti-clot septic venous thromboses. The recommendation of the IDSA guidelines published in 2009 are based on a systematic review published by Falagas *et al* (Eurp J Phar 2007; 557: 93-8), which recommend anti-clotting for their association with a better prognosis. With respect to *S. aureus* bacteremia, the data are scarce, which is why this study is *a priori* of great interest. From my point of view, there are multiple limitations and biases of the analysed cohort. Since all the participants were cancer patients, it seems that including crude mortality at three months does not help obtain the best outcome variable. Moreover, including only patients who had a radiological diagnosis is a recruitment bias, since conducting the Doppler ultrasonography depended only on the discretion of the physician. Slightly over half of the patients showed external signs of thrombophlebitis, and since the radiological study was not systematic, it is impossible to know how many patients with bacteremia without “clear” signs of septic thrombophlebitis were not included in the series for not having a radiological diagnosis. In my opinion, it is unacceptable that a journal of such impact factor did

not show a multivariate analysis about one of the main conclusions of the study. There is an increasing number of studies which demonstrate that the efficacy of the sequential treatment is similar to that of the intravenous antibiotic therapy; therefore, associating a better prognosis to a longer duration of treatment IV (not with the total duration of the treatment) seems complicated, especially when the comparison is made between having received 14-27 days or more than 28 days of IV, where the survival bias is clearly present. The patients with deep thrombosis were anti-clotted more frequently; however, since the study does not show the basal characteristics of the patients who received such treatment and those who did not, it is impossible to draw conclusions about its association with a lower frequency of clinical failure. Furthermore, the authors did not show the incidence of each of the variables that made up the outcome variable, which is a basic aspect, in my opinion. These results should not modify the current degree of evidence for the prescription of anti-clotting of S. aureus thrombophlebitis, which is at clinical discretion based on the risk-benefit ratio.

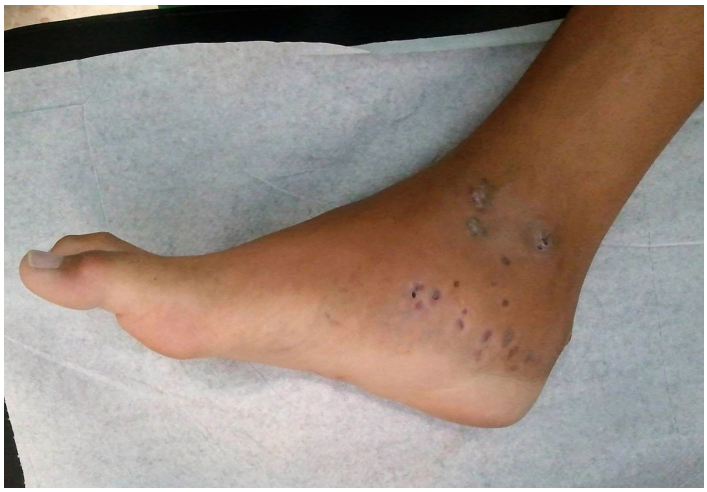
NEWS

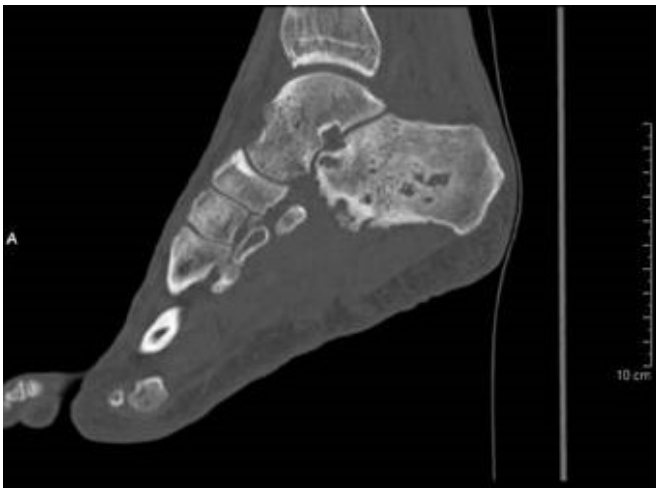
• It is a pleasure to announce that the SAEI Board of Directors has approved that Dr. Alberto Romero Palacios (University Hospital Puerto Real) be the next Editor of Advances in Infectious Diseases. Dr. Eduardo López Cortés will remain on the editorial committee as Assistant Editor. Welcome Alberto!

• 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.

CLINICAL IMAGES





A 23-year-old man who lives in Chiclana de la Frontera (Cadiz, Spain), presented painless swelling in the sole and internal inframaleolar area of the right foot, slowly progressive along months; after one year, he developed violaceous papules of 3-8 mm that occasionally fistulised, draining very small amounts of serous fluid and whitish clots (Figure 1). There was no history of trauma, accidental puncture, fever or other symptoms, and the rest of the physical exploration and analytical tests were irrelevant. The case was evaluated by different specialists and the possibility of neoplasm was considered. The diagnostic uncertainty led to carry out a biopsy of soft tissues in two occasions, with both showing reactive cell proliferation and absence of neoplasm. Radiography and CT results were compatible with osteomyelitis of the calcaneous (Figure 2). Surgery was performed, with corticotomy, bone curettage, sample gathering (microbiology and Anatomical pathology) and implantation of gentamicin-loaded PMMA beads. AP revealed reactive plasmocitosis and osteomyelitis. The cultures of aerobic and anaerobic bacteria, fungi and micobacteria were negative. Later revisions showed some small whitish clot in the fistulous holes, with negative cultures, although the Gram stain allowed visualising branching, gram-positive bacilli in two occasions The treatment established was TMP-SMX (6 months) and amikacin (2 weeks). The evolution was good and one year later the patient walked without pain, the subcutaneous swelling was minimal, he had limited dorsal flexion, and the skin lesions were scarred. This case showed, along with an osteomyelitis due to contiguity, the clinical triad of Madura foot: slowly progressive subcutaneous swelling, fistulous holes and drainage of ball-like clots. Despite the negative cultures, the presence of branching, gram-positive bacilli in the Gram stain finally led to the diagnosis of Madura foot in the form of actinomycetoma. As a relevant epidemiological datum, it was later known that the patient played beach volleyball very frequently, which would justify a gateway for infection through repetitive microtrauma on the bare feet. Madura foot occurs in zones of tropical and subtropical climate. India, the Middle East, Africa and Central and South America are the regions with larger endemic areas, although there are isolated cases in Europe and the USA. Rainfall, soil characteristics and vegetation influence the prevalence of etiological agents. There is also eumycetoma, when this is caused by filamentous fungi, and actinomycetoma, which is caused by actinomycetes. The causing microorganisms penetrate through abrasions of the skin caused by repetitive microtrauma or puncturing by thorns or splinters, generally in people who work bare-footed or with non-protective footwear. The infection generates a slowly progressive subcutaneous swelling, slightly painful, multiple fistulization and drainage of grain-like purulent material, with the final appearance of what has come to be known as “anthill foot” (Figure 1), an image considered pathognomonic, although unfortunately it appears very late.

Diagnóstico: Madura foot.

Note: This case is dedicated to the memory of our colleague and friend Elías Cañas García-Otero, who recently passed away and who we will never forget.

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