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EDITOR´S CHOICE

REFERRAL TO INFECTIOUS DISEASES DECREASES SIGNIFICANTLY THE MORTALITY OF *STAPHYLOCOCCUS AUREUS* BACTEREMIA

☞ ***Referencia Original:*** Association of Evidence-Based Care Processes With Mortality in Staphylococcus aureus Bacteremia at Veterans Health Administration Hospitals, 2003-2014. Michihiko Goto, Marin L. Schweizer, Mary S. Vaughan-Sarrazin et al. *JAMA Intern Med*. 2017;177(10):1489-1497. doi:10.1001/jamainternmed.2017.3958

This is a retrospective, observational study (with all the limitations involved in this design) that included all the patients admitted with *Staphylococcus aureus* bacteremia in the hospitals of the Veterans Health Administration of the USA from January 1st 2003 to December 31st 2014. This is the largest integrated health system in the USA, and provides medical care in 1,250 health care centres, including 172 medical centres and 1,069 outpatient care centres of diverse complexity, which attend to 9 million veterans. The aim of this study was to analyse whether there is a relation between the implementation of medical care processes based on the available clinical evidence (the use of adequate antibiotherapy, echocardiography, consultation with a specialist in infectious diseases) and the mortality associated to staphylococcal bacteremia. The study included 36,868 patients who were admitted in 124 hospitals (97% males, with an average age of 66 years, as is usual in veterans' hospitals). Of the total sample, 52% had methicillin-sensitive *S. aureus* bacteremia. Mortality decreased from 23% in 2003 to 18% in 2014. The frequency of adequate antibiotic administration at the time of the bacteremia shifted from 66% to 78%, the use of echocardiography from 33% to 72% and the referral to a specialist in infectious diseases from 37% to 68% for 2003 and 2014, respectively. After adjusting the results to the characteristics of the patients and the year, having received the three measures was associated to lower mortality ("protective" *odds ratio* of 0.74 if the patient had received an adequate antibiotic treatment, 0.73 if an echocardiography was conducted and 0.61 if the patient was referred to a specialist in infectious diseases). Mortality showed a progressive decrease, inversely proportional to the number of measures performed. The *odds ratio* of having received the three measures compared to none was 0.33.

COMMENT: Dr. Jose Luis del Pozo
Director of the Unit of Infectious Diseases and Clinical Microbiology. Clinical University of Navarra (Pamplona, Spain).

We are all aware that *Staphylococcus aureus* bacteremia has a bad prognosis. The bright side is that we have an important range of improvement for both the diagnosis and treatment of this pathology. The annual incidence of *S. aureus* bacteremia in the USA is 5-40 cases per 100,000 inhabitants. It is predictable that these numbers will increase due to the increasing exposure of the population to health care. Many authors have shown that certain actions are associated to improved survival. For instance, the use of an adequate antibiotherapy in the day of blood culture extraction, the proper control of the infection source, the removal of intravascular devices, and the early screening of an endocarditis through the use of echocardiography, have been correlated to an increase in the survival rate. In this study, the mortality of *S. aureus* bacteremia decreased significantly in the Veterans' Hospitals (USA) throughout the study period (2003-2014), coinciding with the implementation of health care improvement. However, globally throughout this period, one out of four patients did not survive. It is worth highlighting the large sample size of this study (36,868 patients), as well as the significant decrease in the mortality of staphylococcal bacteremia (57%) along the study period. The authors of this work suggest the hypothesis that this decrease in mortality could be due to an improvement in the implementation of certain processes of health care quality. This study shows that the use of an adequate antibiotherapy, the early screening of endocarditis (through echocardiography) and referring to a specialist in infectious diseases lead to an improvement in the survival of the patients. The proper selection of the antibiotic treatment and performing an echocardiography contribute to a better prognosis, since both measures influence the negativisation of blood cultures (we know that the persistence of positive blood cultures is a factor associated to higher mortality), as well as an early detection of endocarditis, which allows for a more effective treatment from the beginning (or even early surgery). The way in which referring to a specialist in infectious diseases reduces mortality may seem less obvious. The specialist may be able to optimise the antibiotic treatment (dose and duration), control the infection source and remove intravascular devices at an early stage. That is, the specialist would be the catalyser for the correct application of the bundle of measures. In the study of López Cortés et al. (2013, Clin Infect Dis), it was shown that the application of a *bundle* of measures (adequate use of antibiotics, source control, and echocardiography) can reduce 5.6% of the mortality of *S. aureus* bacteremia at 30 days after its detection. This was not the objective of the study, although referral to a specialist in infectious diseases could also influence the proper adjustment of the duration of the antibiotic treatment, thus preventing excessive treatment length or suboptimal regimes. It seems clear that the use of *bundles* would be more cost-effective than the use of separate measures, and it would probably be up to the infectologist, the microbiologist and the preventatist to define which are the best measures to be included in these *bundles*.

The study has many limitations, such as its retrospective and observational nature, and the fact that there may be confounding factors. Moreover, the fact that practically all the participants were males limited the generalisation of the results. Finally, this work also shows that there is still room for improvement. It is worth noting that almost 50% of the patients included did not receive some of the three measures analysed. The implementation of quality development programs should be a priority in the daily life of our health care activity.

GUEST COLLABORATOR

EVALUATION OF CEFTOLOZANE-TAZOBACTAM IN COMBINATION WITH MEROPENEN AGAINST *PSEUDOMONAS AERUGINOSA* SEQUENCE TYPE 175 IN A HOLLOW-FIBER INFECTION MODEL

☞ ***Referencia Original:*** Montero M, VanScoy BD, López-Causapé C, et al. Evaluation of Ceftolozane-Tazobactam in Combination with Meropenem against *Pseudomonas aeruginosa* Sequence Type 175 in a Hollow-Fiber Infection Model. *Antimicrob Agents Chemother*. 2018;62(5):e00026-18.

The aim of this study was to investigate the utility of ceftolozane-tazobactam in combination with meropenem against an extensively drug-resistant (XDR) *Pseudomonas aeruginosa* high-risk clone ST175 isolated from a Spanish university hospital. The experimental model selected for this study was a 14-day hollow-fiber infection model. This model allows simulations of clinical exposures of antibiotics, alone and in combination, against known concentrations of the studied strain. During the experiment serial samples for drug concentration and bacterial colony counts (CFU) are obtained. Selection of resistant mutants is also studied. In this study, meropenem alone failed, as evidenced by a final CFU/ml count similar to that seen in the control samples. The ceftolozane-tazobactam monotherapy regimen resulted in an initial decrease, with a value of 2.95 log10 CFU/ml by day 4, but the microorganism regrew and reached an average of 5.24 × 106 CFU/ml. In contrast, administration of ceftolozane-tazobactam in combination with meropenem led to sustained suppression of the bacterial population. The sustained activity of this combination produced a 4.32-log10 CFU/ml reduction and prevented amplification of the resistant subpopulation up to day 14. Simulated drug exposures in this model were considered satisfactory. These data suggest that ceftolozane-tazobactam in combination with meropenem may be a useful combination against XDR *P. aeruginosa*.

COMMENT: Dr. Juan Pablo Horcajada
Infectious Diseases Service, Hospital del Mar, Infectious Pathology and Antimicrobials Research Group (IPAR), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

In the current era of multidrug resistance, clinicians often lack options to treat infections due to antibiotic resistant *P. aeruginosa* isolates. High risk clones of *P. aeruginosa* are a concern in different healthcare centers around the world, and ST175 is of particular relevance in several European countries such as Spain and France. Over the last few years there have been some improvements in the development of new molecules. The new cephalosporin, ceftolozane combined with tazobactam reveals very good characteristics for the treatment of *P. aeruginosa* infections. In vitro studies have shown that ceftolozane appears to be stable against the most common resistance mechanisms in this species. However, although its activity against some XDR *P. aeruginosa* has been demonstrated, it could be limited in some cases. In order to improve the performance of ceftolozane-tazobactam against these extremely resistant bacteria, and trying not to use nephrotoxic drugs as aminoglycosides or colistin, a double beta-lactam combination was studied. This type of combination has been tested with success in carbapenem-resistant Enterobacteriaceae isolates (double carbapenem). The combination of β-lactams may provide stability to Amp C over-expression, which is one of the main resistance mechanisms in *P. aeruginosa*. Therefore it makes sense to try this option. In fact, in this study an excellent cell kill was achieved by associating ceftolozane-tazobactam and meropenem. This efficacy could be related also due to attacking several types of essential penicillin binding proteins (PBP 2 and 3 in *P. aeruginosa*) which can increase bactericidal properties and morphological changes of the bacteria. This is indeed the basis of new emerging therapeutical approaches such as the combination of cefepime with the non-β-lactam PBP-2 inhibitor zidebactam. A part from an excellent cell killing rate, absence of selection of resistant mutants during the 14 days of the experiment is also remarkable and striking. Therefore an additional reason for the enhanced effect observed with this combination is the subpopulation killing of one drug killing the subpopulation(s) resistant to the other drug and viceversa. These innovative *in vitro* observations provide valuable data to expand the research further in this direction and to be evaluated early in clinical use. A high clinical efficacy with low frequency of resistance selection and adverse effects is expected in the clinics with this combination.

GUEST RESIDENT

IS TAFENOQUINE "THE RADICAL CURE" FOR RELAPSES OF *PLASMODIUM VIVAX* MALARIA?

☞ ***Referencia Original:*** A. Llanos-Cuentas, M.V.G. Lacerda et al. Tafenoquine versus Primaquine to Prevent Relapse of *Plasmodium vivax* Malaria. *N Engl J Med* 2019; 380:229-41.

Controlled, prospective, double-blinded, randomised, phase III clinical trial designed to assess the efficacy and safety of tafenoquine with respect to primaquine in terms of preventing relapses caused by *Plasmodium vivax (P. vivax)*. It was conducted between April 30th 2015 and November 4th 2016 in seven clinics of Peru, Brasil, Colombia, Vietnam and Thailand. The total population selected for this study according to the protocol was required to: have a diagnosis of confirmed infection by *P. Vivax* (through direct identification under the microscope), be over 16 years of age with similar demographic and clinical characteristics, and show absence or only moderately deficient activity of the enzyme glucose-6-phosphate dehydrogenase (G6PD), establishing a limit of 30% in women and 70% in men. The patients were randomised at a ratio of 2:1 to receive, under supervision, a single dose of 300 mg of tafenoquine (426 patients) vs 15 mg of primaquine once a day for 14 days (214 patients). Regardless of the group to which they were randomly assigned, they all received an oral treatment of chloroquine (600 mg on day 1 and 2, and 300 mg on day 3). The primary objective of the study was the so-called "Radical Cure", that is, absence of recurrence of malaria, defined as the initial clearing of the parasitemia (no detection of *Plasmodium* in the smear at 6-12h of the treatment), as well as its negative permanence in the evaluation at 180 days. This objective was achieved in 67,0% (CI 95%, 61,0-72,3) of the participants in the tafenoquine group and in 72,8% (CI 95%, 65,6-78,8) of the participants in the primaquine group, setting the risk difference between tafenoquine and primaquine in 4 percentage points in favour of the latter (CI 95%, –4-12), and establishing the non-inferiority margin of tafenoquine in the quotient 1,45. In terms of safety, it was demonstrated that tafenoquine did not have to be suspended due to secondary effects related to it, observing only a decrease in the level of hemoglobin (>3,0 g/dl) in 4 out of 166 patients (2,4%; confidence interval [CI] of 95%, 0,9-6,0) in the tafenoquine group and in 1 out of 85 patients (1,2%; CI of 95%, 0,2-6,4) in the primaquine group, with a difference of 1,2 percentage points between groups (CI of 95%, –2,2-5,0), with no clinical significance.

COMMENT: Dra. Rosario Castilla Ortiz
Fourth-year Internal Medicine Resident at the Puerto Real University Hospital, Cádiz (Spain).

With the promise of "Tafenoquine, Radical Cure", several articles have been published in the last few months in journals of high scientific impact, analysing the advantages and disadvantages of commercialising a new drug. In the present article, a single administration of tafenoquine is presented as the solution to prevent the frequent and unpleasant relapses induced by the characteristic hypnozoites of *P. vivax* malaria. In my opinion, the greater difficulty in adherence to the treatment with primaquine (15 days) compared to tafenoquine (single dose), shown in the subanalysis conducted in a specific part of the Southeastern Asian population, lost relevance when the study concluded that tafenoquine did not achieve non-inferiority with respect to primaquine. I think that, in Medicine, it is ambitious to speak in absolute terms, especially since when we thoroughly break down the analysis of the trials we observe that there are limitations, such as: a small number of patients included in the study sample, inability to generalise the treatment to some patients due to the absence of data about their safety profile (excluded patients with reduced levels of G6PD), and the fact that the study was sponsored and financed by GlaxoSmithKline and Medicines for Malaria Venture, which is the company interested in the production of such drug. My perspective is that we might be approaching what in the future could be an important treatment option to prevent relapses of *P. vivax*, but at the moment the evidence available is not sufficient for making "radical" changes in our current clinical attitude.

NITROFURANTOIN VS FOSFOMYCIN: "TRADITIONAL" IS NOT ALWAYS WORSE.

☞ ***Referencia Original:*** Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. *JAMA*. 2018;319(17):1781-1789.

The use of nitrofurantoin and fosfomycin has increased since the guidelines started to recommend them as first-line therapy for urinary tract infection (UTI). The aim of this study was to compare the clinical and microbiological efficacy of nitrofurantoin and fosfomycin in women with uncomplicated cystitis. This multinational, randomised clinical trial included 513 non-pregnant women over 18 years of age with symptoms of mild UTI, a positive result in the reactive strip, and no colonisation or previous infection by uropathogens resistant to the studied antibiotic. The recruitment was carried out from October 2013 to April 2017 in hospitals and medical centres of Geneva, Switzerland, Poland and Israel. The participants were randomly assigned, at a 1:1 ratio, to either oral nitrofurantoin 100 mg 3 times per day for 5 days (n=255), or a single dose of oral fos-

fomycin 3 g (n=258). At 14 and 28 days after the end of the therapy, the patients were subjected to clinical evaluation with a new extraction of urine cultures. The primary objective was the clinical response at 28 days after the end of the treatment, defined as clinical resolution, failure or undetermined. The secondary objectives included the bacteriological response and the incidence of adverse events. Among 513 patients who were randomly assigned (mean age = 44 years [interquartile range = 31-64]), 475 (93%) completed the trial and 377 (73%) had a confirmed initial positive culture. The clinical resolution up to day 28 was achieved in 171 out of 244 patients (70%) who recieved nitrofurantoin compared to 139 out of 241 patients (58%) who received fosfomycin (12% difference, CI 95%, 4%-21%]; p=0,004). The microbiological resolution occurred in 129 out of 175 patients (74%) compared to 103 out of 163 patients (63%), respectively (11% difference [CI 95%, 1%-20%]; p=0,04). There were very few adverse events, and these were mainly gastrointestinal; the most common were nausea and diarrhea (7/248 [3%] and 3/248 [1%] in the group of nitrofurantoin, and 5/247[2%] and 5/247[1%] in the group of fosfomycin, respectively). Among the women with uncomplicated UTI, the therapy with nitrofurantoin for 5 days, compared to the single dose of fosfomycin, showed a significantly greater clinical and microbiological resolution at 28 days after the end of the treatment.

COMMENT: Dr. Marcos Guzmán

Given the increased resistance to antimicrobials, the guidelines for the treatment of mild UTI are gaining importance in the daily clinical practice. There is still uncertainty about the clinical efficacy of the single dose of fosfomycin, since it is difficult for a single 3 g dose to reach suitable or long-lasting concentrations in the urine, and this could affect its efficacy and the potential creation of microbial resistance. On the other hand, the metanalyses of randomised clinical trials that assess nitrofurantoin for mild UTI suggest that the efficacy of this antibiotic is comparable to that of the most “novel” agents, such as fluoroquinolones, which fosfomycin cannot achieve. The idea that there is little initial resistance to fosfomycin may be inaccurate: regions with an increasing consumption have a proportionally increasing resistance. A longitudinal study carried out in Spain reported an increase in the resistance of fosfomycin from 4% to 11% between 1997 and 2009. With respect to the validity of the study, it describes an open design that can have some level of measuring bias given the subjective primary target. Another important bias is the decentralisation of the laboratory analyses, which could introduce heterogeneity in the microbiological methods, along with the prevalence of different local resistances. However, this study reminds us that we must keep considering “traditional” treatments as valid, since they are equally useful if correctly applied, and they pose a much lower ecological impact. Moreover, the study debunks the idea that “new is better”.

RIFAMPICIN BETTER THAN ISONIAZID IN THE TREATMENT OF LATENT TUBERCULOSIS INFECTION.

☞ ***Referencia Original:*** D. Menzies, M. Adjobimey, R. Ruslami et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults *N Engl J Med* 2018;379:440-53.

This is a multicentre (9 countries), randomised clinical trial that compares the efficacy of an experimental regime of 4 months of rifampicin (RFP) and the usual regime of 9 months of isoniazid (INZ) to treat latent tuberculosis infection (LTBI) in adults. The primary objective of this study was to compare the rates of active tuberculosis (TB) (with microbiological confirmation or clinical diagnosis) at 28 months after the randomization of each group, analysing both the non-inferiority and the potential superiority of RFP. As secondary objectives, the toxicity of the two regimes and their performance were also assessed. The study included adults with a positive result in the tuberculin skin test (TST) at risk of reactivation of a LTBI, who had been instructed to initiate a therapy with isoniazid to treat the latent infection. Of 16,907 patients assessed, 6,063 were randomised (3,016 to the INZ group and 3,047 to the RFP group). The difference in the rates of active TB between the two groups was below 0,01 per 100 patients, with this minimum difference remaining constant in different subanalyses (by protocol, including only patients with a microbiological diagnosis or only those with a clinical diagnosis), which demonstrates the non-inferiority of RFP with respect to INZ. On the other hand, there was no evidence of superiority of RFP over INZ. The number of grade 3, 4 and 5 adverse effects at 146 days after the beginning of the treatment was significantly lower in the RFP group (difference of -1,1 percentage points; 95% CI, -1,9 to -0,4), with toxic hepatitis being the grade 3-4 adverse effect that decreased the most with the use of RFP. Furthermore, adherence to the treatment was higher in the RFP group, with a difference of 15,1 percentage points (95% CI, 12,7 to 17,4).

COMMENT: Dr. Alberto Romero Palacios

There are two specially interesting reasons that justify the need to carry out this study and whose result should pose a change in our clinical practice in the short term. The first reason is the need to increase the current adherence rate of the treatment of LTBI, which seems easy to achieve, as the guideline proposed for the treatment of latent tuberculosis infection

(RFP 4 months) is shorter and less toxic than the one currently accepted (INZ 9 months). The second reason is the need to optimize the treatment guideline in order to improve the eradication of the latent tuberculosis bacillus. The basis of the antibiotic treatment for the prevention of active TB is the elimination of the latent bacterial population, constituted by bacilli with low metabolic activity, with the aim of preventing their later reactivation. Paradoxically, while INZ is very active against a constantly multiplying bacillary population, its activity is marginal against less active bacilli. However, it is precisely in this latent bacterial population where RFP or pyrazinamide have demonstrated their sterilizing activity, which explains the good results obtained in studies conducted with these drugs, in spite of their shorter treatment period. The commented study demonstrated the non-inferiority of RFP with respect to INZ, with two major advantages: lower toxicity and higher adherence rate. To date, this is probably the clinical trial with the strongest evidence on the advantages of using RFP compared to INZ in this clinical scenario. However, as usual, we must read the "fine print": 1) the rate of active infection was lower than expected in both groups (merely 0.1 cases per 100 person-years), which makes the results less robust; 2) the number of HIV patients included in the study was very low (4% of the total, similar in both groups), which limits the generalization of these results in this population; and 3) the study was open label, thus the patients and the prescribing physician knew the assigned drug, although all the objectives were evaluated by an independent panel of experts, who did not know the group that each of the participants belonged to.

SAEI CLINICAL CASES FOR RESIDENTS 2017

PUERPERIO DE EVOLUCIÓN TÓRPIDA: ¿UN HALLAZGO INESPERADO?

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Clinical case

The patient is a 44-year-old woman admitted in the Obstetrics and Gynecology Service with puerperal fever. She works as a cleaner. She had nose bridge surgery, without known allergies or treatment. Examined in 2011 for primary sterility, she was diagnosed with tubal stenosis (Figure 1). In 2015 she was given assisted reproductive treatment (ART) by means of in vitro fertilization (IVF), achieving a bicorial biamniotic twin gestation. The pregnancy had no incidents until week 26 of gestation + 4 days, when she was admitted to the delivery room with the risk of having a premature birth. The uterine dynamics did not yield despite medical treatment, thereby an emergency C-section was performed. A girl and a boy were born, who were admitted to the Intensive Care Unit (ICU) for premature babies; the mother was transferred to the maternity floor, where she presented several fever peaks, treated with Amoxicillin-Clavulanic acid 1gr/8h, and was then discharged. The boy died in the ICU after 18 days. Placenta and blood cultures were negative. One week after discharge she visited her doctor due to a fever over 38ºC, and dysthermic sensation with profuse night sweats and shivers. She did not present any other symptoms. The exploration revealed: preserved general state, blood pressure 99/63 mmHg, heart rate 93 beats per minute and temperature 37.4ºC. Normal auscultation. Soft and depressible abdomen, with no pain, masses or megaly; surgery scar in good condition. Negative first-percussion. Mammary glands with no signs of mastitis. Normal external genitals and vagina. Lochia with no bad odor. Analytically, normal renal function and ions, highlighting PCR of 231 mg/l, hemoglobin: 10 g/dL, Leukocytosis (10580/mm3) with neutrophilia, normal platelet series and clotting. Transvaginal echography described a puerperal uterus with 7-mm endometrial lining, with no visible adnexal pathology; abdominal echography and chest X-ray scan with no pathological findings.

Differential diagnosis

We considered the differential diagnosis of puerperal fever. Puerperium is the time lapsed from the end of birth to the first menstruation after giving birth. During this time, numerous physiological changes occur in women with the purpose of gradually going back to the pre-gravidaric state and establish lactation (1). We thus define puerperal fever when the body temperature is above 38ºC, measured in two time points with a difference of at least 6 hours, from 24 hours to six weeks after giving birth (1,2). Among the risk factors of puerperal fever, we must distinguish between maternal factors, intrapartum factors and post-partum factors, which are specified in Figure (2,3). Among the possible etiologies, we must distinguish between genital and extragenital causes. The genital causes include: endometritis, infection of the episiotomy or laparotomy of the C-section, necrotizing fasciitis, mastitis, septic pelvic thrombophlebitis2. The extragenital causes include: respiratory complications (pulmonary atelectasis, respiratory infection), pyelonephritis, pelvic abscess, thrombophlebitis, thyrotoxicosis,

drug-induced fever, fluid reabsorption and/or hematomas (2).
1. Puerperal endometritis: it is the most frequent cause of fever in puerperium (1,2). In most cases it is produced via ascending route after cervical-vaginal microbial colonisation and it is usually a polymicrobial infection (1). It appears between 1 and 10 days after giving birth (most frequently at day 3 and 4), as a consequence of endometrial tissue infection. Clinical manifestation can be very variable. In addition of fever, it is frequently associated to hypogastric pain, painful movement of the uterus, sub-involuted uterus, persistent metrorrhagia and malodorous lochia (1,2). It is a potentially dangerous clinical condition which, without treatment, can evolve into a diffuse pelviperitonitis and even puerperal septic shock. The most frequently involved microorganisms are (1,3):

- Aerobes (Escherichia coli and other enterobacteria, streptococci, Enterococcus faecalis, Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealitycum).

- Anaerobes (Prevotella spp., Bacteroides fragilis, Peptostreptococcus spp).

We must distinguish between the two forms of manifestation of endometritis. Early endometritis, in the first 24 hours after giving birth, most frequently monomicrobial, is caused by the following agents: Staphylococcus aureus, group A (Streptococcus pyogenes) and B (Streptococcus agalactiae) betahemolytic streptococci, Clostridium spp. Likewise, in 15% of cases, the late form, between the first and sixth week after giving birth, is most frequently caused by previously described agents (4). It is worth mentioning that within the late causes, a possible related cause is Chlamydia trachomatis infection, although it is very rare in our environment.

2. Infection of the surgical wound (C-section, episiotomy): it occurs in approximately 5% of births by C-section, generally at 4-7 days after the intervention (4). The infection-causing microorganisms may come from the very cutaneous flora (S. aureus) or vaginal flora that might have contaminated the uterus or the amniotic cavity (aerobic and anaerobic flora as in puerperal endometritis) (1,2). Episiotomy infection is a rare complication, with a frequency of around 1%.

3. Puerperal mastitis: it appears most frequently at 2-3 weeks after the beginning of lactation (1). The main source of causing microorganisms are the mouth and pharynx of the newborn (streptococci and anaerobes) and less frequently the skin (S. aureus), thereby it is necessary to administer a broad spectrum antibiotic treatment. It is estimated to occur in 2-10% of lactating mothers, but the percentage of those who require hospitalization is much lower.

4. Urinary tract infection. Accute pyelonephritis. It generally occurs at 72 hours after giving birth, but if the birth was vaginal it may occur earlier. With respect to microbiological causes, it is important to consider the most frequent causes of UTI (E. coli and enterobacteria in general, etc.) (1,2).

5. Septic pelvic thrombophlebitis: it is considered as exclusion diagnosis. To be considered only in cases of persistence of the febrile condition after discarding other causes of puerperal fever. It is an infrequent puerperal complication with minimal mortality that may appear after vaginal birth (1/2,000) or after post-partum endometritis (1-2%). It must be suspected in case of persistent fever of unknown origin; it is caused by the combination of three factors: hypercoagulability, vascular lesion by infection or trauma and venous stasis (1).

Evolution

Again, amoxicillin-clavulanic acid 1 gr/8 hours was administered, with disappearance of the fever and oral de-scaling after two days. However, the fever relapsed and the general condition worsened, with non-specific abdominal discomfort, thus gentamicin and metronidazole were added to the treatment and a new blood analysis was conducted: CRP 201 mg/L, procalcitonin 0.11 ng/ml (normal), Hb 10.1 g/dL, leukocytes 6830/mm3 (67% polymorphonuclear), platelets 649,000/mm3, ESR 95 mm/hour. An emergency abdominal computerised tomography (CT) was conducted, which showed heterogenous material in the cervix area and endometrial cavity, with a thickness of up to 50 mm, and retroperitoneal adenopathies of no significant size; the rest of the exploration did not show alterations worth mentioning.
Puerperal curettage was conducted, obtaining fibrinoid material. With the suspicion of perforation and the impossibility of uterus evacuation, a laparotomy was performed with the collaboration of the General Surgery Service.
After opening the parietal peritoneum, it appeared inflamed and had intestinal pack, omentum and the inner and outer side of the uterus firmly adhered to it. There were inflamed small bowel loops with miliary-fibrinoid seeding. Left hysterectomy and fimbriectomy were performed, with the impossibility of performing these in the right side due to strong adherences. The surgical piece showed perforation in the posterior side of the uterus, and occupation by abundant purulent, fibrinoid and necrotic material. (Figure 3)

Meropenem was added to the treatment, removing gentamicin and maintaining metronidazole. New febrile peaks with great general discomfort. Chest-abdomen-pelvis CT showed slight thickening of interlobula septa, subpleural bilateral micronodules and predominance in both upper lobes, to be correlated to granulomatous disease (Figure 4). In abdomen and pelvis, it showed post-surgery changes and free fluid in very low amounts in both gutters, between loops and in the pelvis, without organised collections. Five days later, the Pathologic Anatomy Service reported the finding of granulomata with caseous necrosis, probably related to mycobacterial infection, after analysing the surgical pieces (uterus, left tube and omentum). These data are consistent with the thoracic CT images and compatible with tuberculosis, thereby the patient was administered a treatment with 5 pills/day of Rifater® (isoniazid 120 mg, pyrazinamide 300 mg and rifampicin 50 mg), removing metronidazole and maintaining meropenem, since the surgical wound showed a poor evolution with dehiscence. Negative saliva CRP and culture; IGRA, first one undetermined, second one positive, and positive Ziel-Neelhesen stain in anatomopathological samples. An IGRA test was also requested for the girl, which was positive, thereby the treatment of the infection in the girl was initiated. Two weeks later, after achieving the remission of the fever and the scaring of the surgical wound by applying the Friedrich technique, she was discharged after two months of hospital stay, with follow-up for infectious diseases. The patient followed tuberculostatic treatment for 6 months (2 months of induction + 4 months of maintenance).

Final diagnosis

Tuberculous endometritis. Uterine rupture with secondary peritonitis. Pre-term birth. Wall dehiscence after midline laparotomy.

Discussion.

Genital tuberculosis (TB) is a rare disease in our environment, but still common in underdeveloped countries. This disease is more frequent in young women of countries where TB is endemic and among elder women exposed to TB before the arrival of effective chemoprophylaxis (4). Although most studies mention a 90-100% affectation of the Fallopian tubes in cases of genital TB, other works have described the endometrium as the most affected area. Other cases of genital TB have also been reported in the cervix, ovaries, vagina and vulva (4,5).The actual frequency of female genital tuberculosis is unknown despite the different published data (4,5,6). The literature shows a variable rate of genital tuberculosis, from 2.5% in the Maghreb to 0.005% in developed countries. The genital form is usually asymptomatic and constitutes a finding in fertility analyses (10% of primary sterilities), in the analysis of surgical pieces or in the examination of echographic findings (hydrosalpinx, adnexal masses or endometrial hypertrophies), although in general we can assert that it is a disease of varied symptoms (from asymptomatic, as already mentioned, to generally presenting infertility, menstrual disorders, pelvic pain, leukorrhea, pelvic mass, ascites and fever) (4). Genital TB is usually caused by secondary hematogenous dissemination due to an extragenital infectious process, mainly of pulmonary origin (5), although the clinical manifestation may not appear until 10 years after the initial seeding of the genital tract (4,5). In our case, there was no personal history of TB or lung involvement; however, when rehistorising the patient, she mentioned a pneumonic infectious process in a previous trip to Cuba 20 years ago, whose resolution required a long time. The diagnostic approach must be conducted with the clinical history, physical exploration, cytology, IGRA or Mantoux test, chest X-ray scan, echography, hysteroscopy, laparoscopy, and bacteriological and histological analysis. The diagnosis must be confirmed with the menstrual culture and with the biopsy of the endometrium, which is positive in almost 80% of cases (6,7). In the histopathological analysis, finding granulomatous lesions does not confirm the diagnosis6, since other diseases may affect the female genital parasite, producing a similar appearance; these diseases include sarcoidosis, brucellosis, tularemia and reaction to foreign bodies, which highlights the importance of and need to carry out cultures. Laporoscopic findings vary according to the rate and prevalence of TB. In pelvic or peritoneal TB there is an increase of CA 125, thereby the differential diagnosis must be done with ovary cancer. Hysterosalpingography, as part of evaluation tests in cases of infertility, may show the typical appearance of tuberculous infection, such as wire thread in isthmic position, or in the shape of a golf club or mass in the ampullary region, bulbous horn or pearl necklace, as well as obstruction or hydrosalpinx (6,7).A final diagnosis cannot be established from characteristic features in the hysterosalpingogram or laparoscopy. Due to the paucibacilar nature of genital TB, the diagnosis by mycobacterial culture and histopathological examination have limitations and low detection rate. Therefore, other diagnostic methods have been developed, such as polymerase chain reaction (PCR) 6,7, a sensitive and quick technique that can be carried out in any sample. PCR has the advantages of requiring minimal amounts of DNA and can be reported in a shorter time; in addition, it can be used to monitor the therapeutic response7. The treatment is the same as that for pulmonary TB (4,5), with a combination of antituberculosis drugs, usually 3 or 4 drugs, for 6 months. Surgery is indicated if the symptoms or the physical exploration suggest persistence or recrudescence of the disease, despite the adequate medical treatment, or if the analyses show resistant organisms. The ultimate surgical treatment is hysterectomy with double adnexectomy, and must be programmed at least 6 weeks after the end of the medical treatment (4,5). Given the difficulty of its diagnosis, due to its non-specific symptoms and even asymptomatic nature, this entity must be considered in the differential diagnosis

and adequate tests must be requested for its confirmation. Moreover, we must mention congenital tuberculosis, given the development of our clinical case. This entity presents a diagnostic challenge. The symptoms are generalised and non-specific. The immunological diagnosis (IGRA test) is frequently negative in the first weeks of life and the infection is produced by vertical transmission (either hematogenously, by propagation or by inhalation of infected amniotic fluid in the uterus) (8,9,10). A literature review of published cases to this respect showed that over half of the mothers were not diagnosed until after the diagnosis of their babies was confirmed (8). Although very rare in developed countries, this case demonstrates that female genital tuberculosis must be included in the differential diagnosis of some gynecological syndromes, especially in cases of sterility. The treatment of congenital TB may be compared to that of acquired TB. Corticoids are recommended in case of meningeal involvement or obstruction of the airway and in miliary disease (8,9,10). Lactation should not be contraindicated if the mother and the child receive an adequate treatment8. Genital tuberculosis is an important cause of infertility, especially in underdeveloped countries. However, it is rare in the developed world and its diagnosis is challenging. The combination of diagnostic methods can improve the identification of cases and help to avoid transmission. Congenital TB is an unusual form of manifestation, with high morbimortality, that requires a high rate of suspicion for its diagnosis and treatment.

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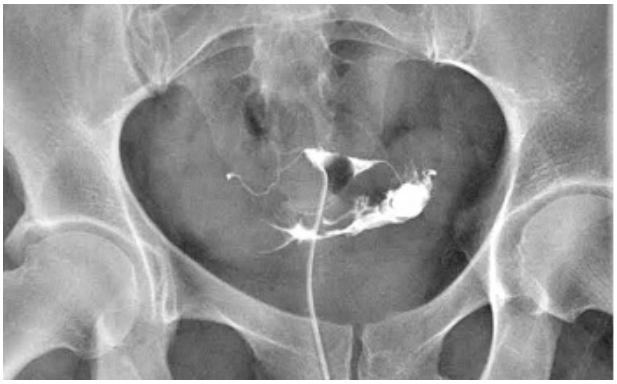


Figure 1. Hysterosalpingography: distal obstruction of the right tube; permeable left tube with passage of the iodised contrast to the abdominal cavity.

RISK FACTORS

MATERNAL
- Maternal immunosuppression (diabetes mellitus, immunosuppressive treatment, corticotherapy, HIV, systemic diseases – systemic lupus erythematosus, scleroderma-).
- Positive group B streptococci.
- Obesity (surgical wound infection).

INTRA-PARTUM
- Duration, time of amniorrhexis, prematureness.
- C-section (urgent > childbirth course > elective).
- Instrumented birth.
- Manual delivery.
- Manual revision of the uterine cavity.

POST-PARTUM
- Anemia (Hb< 8g/dl).
- Seroma/hematoma of the surgical wound, drainage, insufficient cleaning/care of the surgical wound.

Figure 2. Risk factors of puerperal fever.

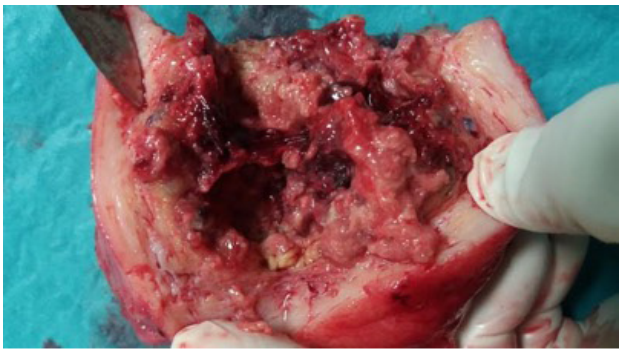


Figure 3: Hysterectomy: remains of fibrin and purulent material in the endometrial cavity.

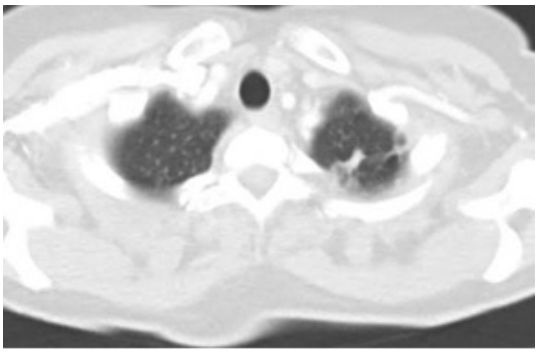


Figure 4: Thoracic CT: calcified micronodule and fibrotic tracts in the left upper lobe.

NEWS

• AEI is open to everyone who is interested in infectious diseases. If you want to collaborate with the journal, you can contact Dr. Alberto Romero Palacios (alberpalacios@hotmail.com).

• We remind you that the section "Clinical Images" is open to all readers. If you want to publish a case in the SAEI or AEI websites, you can send an email to Dr. Domínguez (adomin60@gmail.com) with a brief clinical summary.

• **The best of CROI 2019.** March 12th in Seville (Spain). More information in the following link: http://www.saei.org/evento/ver/id/125/titulo/lo-mejor-del-croi-2019.html

• **XII debate day about controversies in Infectious Pathology**. March 14th in Córdoba (Spain). More information in the following link: http://www.saei.org/evento/ver/id/144/titulo/xii-jornadas-de-debates-sobre-controversias-en-patologia-infecciosa.html

• **IV day of Tuberculosis 2019.** March 20th in Seville, Spain. More information in the following link: http://www.saludpublicasevilla.org/index.php?option=com_content&view=article&id=66&Itemid=196

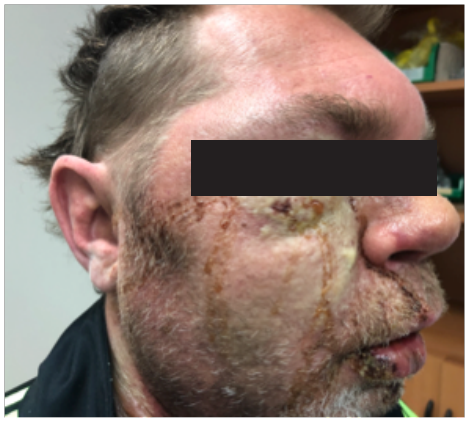
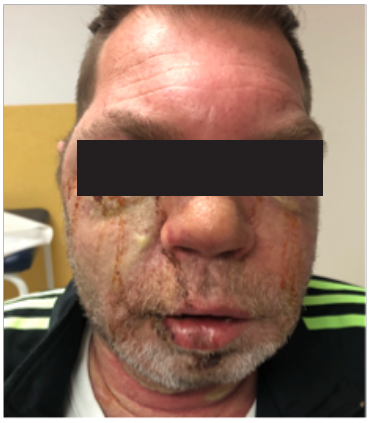
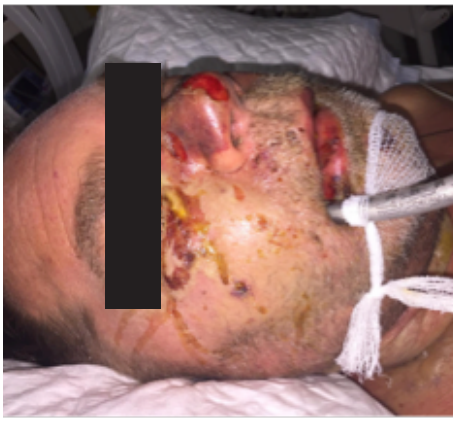
• **III GAEVIH course** (Andalusian HIV research group) about HIV updates 2019. March 22nd-23rd in Antequera (Málaga, Spain). More information in the following link: http://www.saei.org/evento/ver/id/145/titulo/iii-curso-gaevih-sobre-actualizacion-en-vih-2019.html

• **I SATO-SAEI course** (Andalusian Society of Traumatology and Orthopedics – Andalusian Society of Infectious Diseases) and **X forum of Osteoarticular Infectious Pathology**. March 22nd-23rd in the Regional University Hospital of Málaga (Spain). Registration is free and its formalization must be done through the SATO website (https://www.portalsato.es)

• **VII GEMICOMED days** (Medical Mycology Research Group of the SEIMC). March 29th in Madrid (Spain). More information in the following link: https://seimc.org/contenidos/gruposdeestudio/gemicomed/reunionesyeventos/gemicomed-rye-2019-VII_ReunionCientifica.pdf

• **Principles and practice of PROA** (organized by **GEIRAS**, the Healthcare-Related Infectious Diseases Research Group of the SEIMC). June 6th, 7th and 8th in Torrecaballeros, Segovia (Spain). More information in the following link: https://aymonproa.acblnk.com/envio/ver/673540/VjlfKnSHdDNYYH4rV7P22EdCM7XaRtjE57ahGjzu00Zo3GvrO2bdWysoez/VjlfKnSHdDNYYH4rV7P22EdCM7XaRtjE57ahGjzu00Zo3GvrO2bdWysoez/

CLINICAL IMAGES

38-year-old patients from Sweeden on vacation at Vejer, whose only medical history of interest is a HIV infection on anti-viral treatment and good immunovirologic control. He went to ER 3 days before the pictures were taken, suffering from a very painful, scabby lesion in the lower lip with a perilesional inflammatory component. The patient said to have had similar episodes in the past, although less symptomatic. Suspecting a relapse of herpes labialis and with the aim of reducing the inflammatory component, he was prescribed a treatment of oral corticoids (deflazacort 30), telling him to wait 3-4 days to determine his evolution. At the third day (when the pictures were taken), he went again to ER with high fever, poor general state and very intense pain in the face. Exploration showed generalized facial cellulitis that extended from the neck to the forehead, with indurated edema and numerous purulent blisters that festered upon pressure. Palpebral inflammation did not allow the patient to open his eyes. The vital signs showed that the patient was hypotensive (90/68 mmHg), tachycardic (110 bpm), and had a mild resting tachypnea (16 rpm). The blood analysis showed leukocytosis (18,500 leukocytes, 80% PMN) with high PCR (25 mg/dl) and mild kidney failure (urea 90 mg/dl, creatinine 1.7 mg/dl). After extracting the blood cultures and collecting the samples of the facial blisters, an empirical treatment was initiated with Meropenem, Linezolid and Clindamycin. The quick progression of cellulitis to the neck (objectivable during the 2 hours that the patient spent in ER), forced his transfer to the ICU for orotracheal intubation, due to the risk of external compression of the airway. Finally, the patient was transferred to the Plastic Surgery Unit of the Puerta del Mar University Hospital, where he was intervened with urgency, debriding and liberating the most affected areas. The blood and facial pus cultures showed Streptococcus pyogenes. The patient was discharged after 15 days of hospital stay.

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