has the largest number of members followed closely by the Asthma area.[3]

Some studies have analyzed the socio-economic characteristics of EC members of scientific journals from different specialist areas. These studies have noted an increasing trend in the number of women on ECs in recent decades, although the number of men is still much higher.[4–10] There is also a lack of international representation on ECs. EC members from developed countries are highly represented compared to those from low-middle-income countries.[11,12] Even so, studies on this subject are tremendously scarce.

The number of members on some of these ECs should also be taken into account. Some exclusively online magazines have ECs of between 200 and 300 people, which can give a misleading view of the presence of SEPAR people on these ECs.

This study has a number of important limitations. The first of these is that only respiratory journals were analyzed, so the picture is skewed, as many SEPAR members may sit on ECs of journals in other specialist areas, such as infectious diseases, pulmonary circulation, internal medicine, public health, or surgery and transplantation, and therefore were not taken into account in this study. The fact that membership of the EC of Archivos de Bronconeumología was excluded from the calculations may also be debatable. However, we believe that its inclusion would have "inflated" the results favorably.

It is worth considering whether these data are good or bad, or what the reasons for this modest presence may be. In a way, it is somewhat contradictory that the Spanish respiratory medicine has a top quartile journal, Archivos de Bronconeumología, which reflects the importance of the research done in our country, yet our presence on the ECs of respiratory system journals is so low. An alternative explanation for this limited presence may be the fact that in the vast majority of cases, EC membership is unpaid and has little weight when collecting curriculum points for public examinations. It is a time-consuming job, and many members could have declined a position on an EC for this reason, despite being invited for their scientific merits.

We are of the opinion that this study should be repeated after some time to determine if there is any change in the proportion of SEPAR members on these ECs. In addition to the academic and research acclaim that these ECs garner for their members, these positions are a general indication of the recognition and prestige given abroad to a medical discipline.

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Neutropenia secondary to tuberculosis treatment☆

Neutropenia secundaria al tratamiento de la tuberculosis

To the Editor:

We report the case of a 43-year-old Dominican man with no medical history or regular medication who was admitted for a 1-month history of fever in the evening, low back pain radiating to the lower limbs, and constitutional symptoms. Computed tomography showed left laterocervical lymphadenopathies, central lobular nodules in the middle pulmonary lobe, collections in the left psoas-iliac muscle extending to the obturator and adductor, and L1–L2 spondylodiscitis. Magnetic resonance imaging revealed intravertebral collections in L1 and L2 and another perivertebral collection.

Ultrasound-guided puncture of the psoas abscess was performed. The sample was sent to the microbiology lab for culture and auramine staining: sputum smear revealed 1–9 acid-alcohol-resistant bacilli per 10 fields at 250X. PCR was positive for *Mycobacterium tuberculosis*, and no rifampicin resistance was detected by GeneXpert MTB/RIF. The adductor muscle abscess was drained surgically. HIV serology was negative.

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Treatment began with isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z), and continued for 3 months due to the extensive involvement and the existence of undrained intra- and perivertebral collections. Culture of the abscess grew HREZ and streptomycin-sensitive *Mycobacterium tuberculosis*. The patient tolerated treatment well, with normal liver function and blood counts.

At the end of the third month, E-Z was discontinued, and H-R was maintained. At month 5 of treatment, the patient presented neutropenia that progressed to 500 neutrophils/μL (2,780 leukocytes/μL) by month 6. He also developed a severe adverse reaction to granulocyte colony-stimulating factor (sudden dyspnea). Initially, neutropenia due to R was suspected, so this drug was withdrawn and, in order not to continue treatment with H alone, E and moxifloxacin (MFX) were added. Neutropenia worsened, falling a week later to 370 neutrophils/μL. All treatment was discontinued, and a bone marrow aspirate was performed that ruled out central neutropenia. PCR for *Mycobacterium tuberculosis* in the bone marrow was negative.

Neutropenia resolved 1 week after complete discontinuation of treatment. Only R was restarted because it was the most important drug in the treatment of tuberculosis[1] and because the patient's neutropenia had worsened with H-E-MFX. In order to determine whether R was also involved in neutropenia, it was prescribed in increasing doses until the ideal dose was reached within a week. Two weeks after this reintroduction, the patient once again showed a progressive reduction of neutrophils, that fell to 570/μL, so R was definitively discontinued.

Three weeks later, once the blood count was normalized, H was reintroduced. There were no incidents with respect to blood count and E-MFX was added. The combination of these 3 drugs was maintained for the following 4 months, and neutrophil levels remained above 800/μL, allowing for a total of 12 months of treatment. At all times the neutropenia was asymptomatic and the patient remained afebrile. The collections on the magnetic resonance imaging disappeared and neutropenia resolved after completing treatment. Given the good clinical and radiological progress, drainage of most of the collections, treatment with R for almost 6 months, and the persistent neutropenia, we decided not to prolong the treatment for 18 months, as recommended in cases of R intolerance.[2]

Treatment of tuberculosis requires combinations of 3–4 drugs for long periods of time (6–9 months is recommended in the case of vertebral involvement).[2] The combined use of several drugs increases the chances of adverse reactions. In the case of the standard HRZE scheme, hepatotoxicity is the most frequent adverse effect, but there are other less common but serious issues, such as hematological events and, in this case in particular, neutropenia.[3]

The incidence of leukopenia observed in the seminal studies on H-R regimens is between 2% and 10%,[4,5] but less than 1% in the specific case of neutropenia.[4] In fact, since Ferguson first described the association between H and neutropenia during treatment in a patient with tuberculosis in 1952,[6] isolated cases have been reported.[7]

Among the first-line drugs, H may be the one most frequently associated with neutropenia,[8] but it has also been described with R[9] and E[10]; among second-line drugs, linezolid is the one most frequently involved.[3]

It should be noted that the onset of neutropenia in this patient was late, which justifies the recommendations of the SEPAR 2010 guidelines for performing complete blood counts both at the beginning of treatment and at months 2, 4, and 6.[11] The fact that it occurs after a long exposure time suggests an immune mechanism rather than direct bone marrow damage.[12]

Different courses have been described in the literature: in some cases, the therapeutic regimen had to be modified, while in others, neutrophil concentrations stabilized at safe levels, so treatment could be completed. In fact, in the study by Lee et al. of 825 patients with no hematological history who started first-line treatment for tuberculosis, 185 developed leukopenia, 109 of whom continued treatment: neutropenia resolved during treatment in 30% and in the rest, it normalized after completion.[13] The use of colony-stimulating factors to induce medullary neutrophil production has been proposed as an alternative.[14]

Our patient's neutropenia reappeared unequivocally after isolated reintroduction of R and in the absence of other drugs, so its association with neutropenia can be defined as "certain" according to the WHO causality classification.[15] However, his neutrophil count did not completely normalize until the antituberculous treatment including H was completed, so it is reasonable to think that both drugs contributed to the etiology of the neutropenia.

In short, our intention is to warn of this hematological toxicity that may appear with tuberculosis treatment (especially H and R) and to share our particular experience on its progress and management, in case it could be of help to the rest of the scientific community.

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Combined Diaphragm and Limb Muscle Atrophy Is Associated With Increased Mortality in Mechanically Ventilated Patients: A Pilot Study

La combinación de atrofia del diafragma y atrofia de los músculos de las extremidades se asocia a un aumento de la mortalidad en los pacientes con ventilación mecánica: un estudio piloto

Dear Editor,

Patients admitted to the intensive care unit (ICU) are at high risk of developing peripheral and respiratory muscle compromise.[1–3] ICU-acquired limb muscle weakness (ICUAW) and ventilator-induced diaphragm dysfunction (VIDD) are the hallmarks of myopathy affecting critically ill patients. The presence of either ICUAW or VIDD is associated with poorer outcomes, including prolonged mechanical ventilation, ICU stay and mortality.[1,2,4–8] Muscle wasting plays a central role in the development of skeletal muscle weakness. Limb and respiratory muscle atrophy occurs rapidly in critically ill patients.[9,10] Few studies have analyzed the development of ICUAW and VIDD in the same subjects, and reports describing the evolutionary pattern of muscle wasting affecting both peripheral and respiratory muscles in critically ill patients are scarce.[2,11–15] Dres et al. demonstrated that limb muscle and severe diaphragm weakness have a cumulative negative impact on patients' outcome.[12] Whether peripheral muscle and diaphragm atrophy also have a cumulative impact is unknown.

The aim of this pilot study was to describe the evolutionary pattern of limb muscle and diaphragm thickness in critically ill patients requiring mechanical ventilation, and to determine whether the combination of limb and diaphragmatic atrophy has a cumulative impact on patients' outcome.

Thirty-two adult patients admitted to ICU and requiring invasive mechanical ventilation were included. Diaphragm, mid-upper arm, mid-forearm and mid-thigh muscle thickness were measured by ultrasound on admission and repeated on days three and seven (Supplementary Fig. 1). Diaphragmatic atrophy was defined as a decrease in diaphragm thickness ≥5% from baseline. Limb muscle atrophy was considered when any of the peripheral muscles had a decrease in thickness ≥5% from baseline. Subjects associating diaphragmatic and limb muscle atrophy were considered to present combined muscle atrophy.

Categorical variables were reported as absolute numbers (percentage) and compared using Chi-square test or Fisher exact test. Continuous variables were expressed as mean ± standard deviation if normally distributed, or median (25th, 75th percentile) if not. Student *t* test was used to compare initial muscle thickness between groups. Mann-Whitney *U* test was performed to compare muscle thickness change from baseline between atrophy and no-atrophy groups at each time point. The Spearman correlation was used to analyze bivariate correlations. A P value < 0.05 was considered statistically significant. A more detailed description of the methods is provided in the Supplementary material.

Patients' characteristics are summarized in Supplementary Table 1. Median time on mechanical ventilation was 11 (5, 13) days and ICU mortality was 25%. During the first week, patients were mostly ventilated in assisted/controlled modes. All 24 patients that survived after ICU admission were weaned from mechanical ventilation (20 extubated, 4 tracheostomized after the first week) and discharged alive from the hospital. Mean baseline diaphragm thickness on admission was 1.7 ± 0.5 mm. This measurement was slightly higher in men *versus* women (1.9 ± 0.4 mm *vs.* 1.5 ± 0.6 mm, $P = 0.066$), but not statistically significant. Diaphragm thickness evolution was explored in 29 subjects. Twenty (69%) subjects developed diaphragm atrophy during the first week after ICU admission. In this group of subjects, diaphragm thickness change from baseline was −10.3% (−17.8%, 0.0%) on day 3 and −15.8% (−30.7%, −5.5%) on day 7 ($P = 0.010$ and $P = 0.003$ compared with subjects without diaphragm atrophy, respectively; Fig. 1A).

Mean arm, forearm and thigh baseline muscle thickness were 2.49 ± 0.62 cm, 3.24 ± 0.53 cm and 3.01 ± 0.54 cm, respectively. Overall, men presented higher peripheral muscle thickness than women on admission (arm: 2.60 ± 0.68 cm *vs.* 2.20 ± 0.33 cm, $P = 0.033$; forearm: 3.34 ± 0.55 cm *vs.* 2.97 ± 0.38 cm, $P = 0.079$; thigh: 3.19 ± 0.45 cm *vs.* 2.56 ± 0.51 cm, $P = 0.002$). Evolution of arm muscle thickness was explored in 31 subjects, 12 (38.7%) of whom developed atrophy. Evolution of forearm and thigh muscle thickness could be measured in 29 subjects. Forearm atrophy was observed in 11 (37.9%) subjects, while 10 (34.5%) subjects acquired quadriceps atrophy. The change in limb muscles thickness was significantly different among patients with or without atrophy (Fig. 1B–D). When considering the evolution of all three peripheral sites, 19 (61.3%) patients developed limb muscle atrophy affecting at least one of the explored muscles.

Thirteen (44.8%) subjects presented an association of diaphragmatic and limb muscle atrophy (Fig. 1E). The combination of respiratory and limb muscle atrophy was the most common profile (44.8%), as compared to patients presenting only diaphragmatic atrophy (20.7%), only peripheral muscle atrophy (13.8%) or no atrophy at all (20.7%). No significant correlation was found between the maximum decrease in diaphragm and limb muscle thickness ($r_s = 0.336$, $P = 0.075$).

Demographic, clinical or therapeutic characteristics and baseline muscle thickness were similar among patients who developed atrophy and those who did not (Supplementary Tables 2–4 and Supplementary Fig. 2).

Baseline thickness of all the explored muscles was also similar between survivors and non-survivors (Supplementary Fig. 3). Duration of mechanical ventilation, ICU and hospital length of stay was not significantly different between subjects with or without