

Tuberculosis and COVID-19: a dangerous liaison

Less than a year after its global emergence, SARS-COV-2 has already displaced *Mycobacterium tuberculosis* as the main cause of death from a single infectious agent. Although this datum is in itself disturbing, the most severe and lasting consequences of this new pandemic will perhaps not be medical but socioeconomic. Indeed, according to an estimate by the United Nations University, COVID-19 would have devastating effects in the poorest countries in Africa, Southeast Asia, Latin America¹. These are precisely the countries with the highest burden of tuberculosis (TB), a social disease associated with overcrowding, migration, and malnutrition. Exposure to people living with TB in poor households increases dramatically during quarantine. Furthermore, limitations in both personal mobility and access to medical services cause delays in the diagnosis of TB and irregularities in its treatment. Added to this, the pauperization produced in the context of the current pandemic could lead to a drastic increase in the incidence of TB^{1,2}.

In Argentina, the average TB burden is moderate, with notable regional differences. The decline in incidence, sustained for decades, has reversed since 2013, when it began to increase by 2.3% annually. The rates for 2018 and 2019 were 23.6/100 000 and 26.1/100 000. In 2019, a total of 11 741 TB cases were reported. The highest rates were registered in Salta, Jujuy and in the city of Buenos Aires (CABA) with 60.7, 48.8, and 38.9 cases per 100 000, respectively³. In the CABA, 74% of the notifications come from the public sector (most of these are from the Muñiz Hospital and 12% from university centers, especially the Vaccarezza Institute). About 50% of the patients diagnosed with TB in the CABA are not residents of the city, but consultants from the suburbs. TB is still prevalent in young adults, pointing to recent transmission in the economically active population. Follow-up information is available for only 48% of the cases, a shortfall that is related to the high proportion of patients from the suburbs. Of those with available information, 67% completed treatment, 21% abandoned it, and 6% died⁴.

Regarding TB and COVID-19 coinfection in our country, Palmero et al.⁵ recently reported a series of 23 cases diagnosed in March-June in 5 hospitals in the CABA, 13 of them in the Hospital Muñiz-Instituto Vaccarezza. Four patients were under 16 years of age, 10 were born in Argentina, 7 in Bolivia, and 5 in Peru. As many as 17 of the 23 came from poor neighborhoods and in 15 the diagnosis of TB was suspected from the images obtained to assess pulmonary involvement by COVID. Six patients reported a recent history of previous anti-TB treatment, incomplete in 4 of them. In this case series, the authors highlight: (i) the high frequency of TB, almost 40 times higher than the TB rate in the CABA; (ii) the high proportion of residents of poor neighborhoods and male migrants from neighboring countries; and (iii) a mortality 3-4 times higher than that attributed to COVID-19 in Argentina. In this issue of *Medicina (B Aires)*, Vanzetti et al.⁶ report three other cases of TB and COVID-19 coinfection, also from the CABA. These case series from Argentina add substantial evidence to the largest series available in the literature, which consists of 49 cases of this association diagnosed in eight other countries and three continents⁷.

Little is known yet about the interaction of SARS-COV-2 with the human immune system. Exposure can cause from a self-limited asymptomatic viral infection to a potentially fatal acute illness. In contrast, *M. tuberculosis* is an obligate human intracellular parasite that has coevolved with its host for millennia, and produces from a lifelong latent bacterial infection to a chronic emaciating disease. Despite these differences, both pathogens share some characteristics. Both are transmitted by air, affect the lungs,

usually present with nonspecific conditions, and share social determinants⁸. Kumar et al.⁷ point out five reasons why the clinical management of coinfection may be hindered: (i) TB may go unnoticed due to the non-characteristic clinical presentation of both diseases and the absence of radiological lesions specific to TB; (ii) the virus itself or its treatment with immunomodulators such as dexamethasone can reactivate latent TB; (iii) a pre-existing tuberculous lung lesion can result in COVID-19 clinical miscategorization; (iv) coexisting active TB may predispose to severe COVID-19 disease; (v) interaction may occur between drugs used to treat both diseases (e.g. rifampicin and lopinavir / ritonavir) as well as cumulative liver toxicity.

TB is not considered a common comorbidity of COVID-19. Although there is some information on TB-COVID-19 coinfection in the medical literature, the scientific evidence on the potential influence of COVID-19 on the course of TB and TB services is still meager. To address these issues, the Global TB Network has launched, with the support of WHO, a global multicenter cohort study on the clinical course and evolution of people with COVID-19 and TB⁹. The questions raised in the project are the following: 1) Does COVID-19 increase the risk of reactivation of TB?; 2) What risk of TB mortality can be attributed to COVID-19?; 3) What are the other determinants of mortality in patients co-infected with TB and COVID-19?; 4) Does BCG vaccination protect?; 5) Do patients co-infected with TB and COVID-19 require different clinical management? If so, what kind of handling? 6) What influence will COVID-19 have on TB services in the coming years? 7) Are patients with post-TB sequelae at higher risk of contracting COVID-19? As of October 2020, 132 centers from 36 countries, including leading centres from Argentina, had joined the study⁹.

In the present circumstances, when faced with a suspected case of COVID-19 with nonspecific respiratory infection and prolonged or atypical clinical evolution, TB should be investigated in high-prevalence areas, especially in population groups at risk of TB.

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