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Editorial

The Future for Pediatric Cystic Fibrosis, After the Emergence of Highly Effective Modulating Therapy

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Therapy with cystic fibrosis transmembrane conductance regulator (CFTR) modulators has impacted the pulmonary, pancreatic, and nutritional function of patients with the disease, substantially improving their quality of life [1]. The first approval of triple therapy with elexacaftor/ivacaftor/tezacaftor (ETI) initially included cystic fibrosis (CF) patients aged 12 years or older [2]. The results of ETI therapy were so favorable in efficacy and safety that studies were subsequently published that allowed the indication of the therapy to be lowered to patients older than 2 years, and it is currently called high-efficacy modulating therapy (HEMT) [3,4]. This change in the disease paradigm will bring a series of challenges for patients, their parents, and multidisciplinary teams that deserve to be discussed.

The increasing access to HEMT has improved the survival and fertility of many young women with CF, which will require genetic counseling teams in clinical follow-up programs. Furthermore, the increased pregnancy rate among CF patients treated with modulators and the transplacental or breastfeeding transmission during the neonatal period could explain why carriers of the disease do not present with the usual classic symptoms or test negative in newborn screening [5].

HEMT achieves normalization of forced expiratory volume in the first second in spirometry, which has led pediatric CF groups to seek more sensitive respiratory functional tests such as impulse oscillometry, lung clearance index in multiple breath nitrogen washout, and magnetic resonance imaging, increasing the costs and complexity of follow-up [6-8]. Although it does not completely eradicate them, HEMT has been shown to reduce the common pathogens in patients' bronchial secretions and paranasal sinuses. Furthermore, patients on HEMT experience a change in the composition of their respiratory microbiota, resulting in a more diverse and healthier microbiome, which will likely be accompanied by a significant decrease in antibiotic indications and regimen changes in the future [9]. A clinical situation that raises an ethical dilemma is whether or not to perform lung transplantation on children with CF and severe lung involvement in the end-stage who have already achieved access to the HEMT. Regarding this situation, there are already reports recommending that CF teams involve the family in the clinical discernment process for shared decision-making, respecting the autonomy of the patient and their family [10].

HEMT has shown benefits in endocrine pancreatic function, improving glycemic control in patients, which will likely delay the onset of disease-related diabetes. The effect appears to be greater the earlier in life the treatment is initiated [11]. HEMT has begun to dispel the myth that exocrine pancreatic insufficiency was irreversible. Although the changes are not as pronounced as those seen in pulmonary function, medium-term follow-up cohorts using HEMT have demonstrated a reduction in digestive symptoms, an increase in fecal elastase, and a decrease in intestinal inflammation as measured by fecal calprotectin [12-14]. This is undoubtedly a great advance; however, there is a real risk that patients, perceiving fewer digestive symptoms, may lose adherence to pancreatic enzymes, which will require

individualized enzyme adjustment protocols. Nutritional status, as measured by weight in kilograms or body mass index (BMI) z-score, has also improved in all HEMT studies. It remains to be determined whether children on this therapy should continue to be recommended to have a BMI greater than or equal to the 50th percentile for age (z-score greater than or equal to 0 for age), or whether an adjustment of nutritional goals is required to avoid overweight or obesity, which could become problems for them in the future [15].

The mental health of patients receiving HEMT has shown positive changes due to improved lung function, better physical capacity, and a decrease in symptoms. This has also been observed in their parents after they complete the long and uncertain journey that leads them to access this therapy for their children [16]. However, mental health teams must be vigilant for the emergence of adverse effects on sleep, conduct, and behavior that could be associated with the therapy [17,18].

Despite all the well-known benefits of HEMT and its significant impact on the health of CF patients, substantial inequities in access remain. Low- and middle-income countries and ethnic-racial minorities with rare mutations who lack access to HEMT require urgent support from government health systems and the pharmaceutical industry; otherwise, this gap will continue to widen in the future [19].

Finally, with the emergence of HEMT, some countries have already set an example by designing modern care models, with resources and follow-up strategies that allow them to meet the new needs of patients, as well as the health personnel who care for them [20].

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