Can we use noninvasive respiratory therapies in COVID-19 pandemic?☆

¿Podemos usar terapias respiratorias no invasivas en la pandemia COVID-19?

Dear Editor,

It is well known that non-invasive respiratory therapies (NITs) have transformed the management of patients with acute respiratory failure of various causes. Techniques such as non-invasive mechanical ventilation, continuous positive airway pressure through a nasal mask, or more recently, high-flow therapy have shown to be effective in reducing the rate of intubation and mortality in patients with hypoxemic and hypercapnic failure, in the absence of intubation criteria. NITs allow an early start of treatment, combine different techniques of ventilatory support, improve patient tolerance and well-being, save time for medical treatment to take effect and, ultimately, decrease the need for intubation and admission to intensive care. In addition, they allow the continuity of treatment in those patients who are discharged from these units and persist with respiratory failure in the ward.[1]

The COVID-19 pandemic has called into question the therapeutic potential of NITs, by giving greater emphasis to the risk of pathogenic agent spread which, on the other hand, is a problem that has been known for years.[2] Based on this, NITs have been considered high risk procedures in COVID-19 and there is a school of thought recommending not to use them.[3] The technical document on the clinical management of patients with COVID-19 disease, published by the Spanish Ministry of Health on 3rd March 2020, recommended that they should be avoided.

The application of these criteria has the risk of posing a therapeutic dilemma where clinicians have to choose between administering invasive ventilatory support or giving conventional oxygen therapy to a patient. Patients may not receive adequate treatment until it is time to be intubated and connected to invasive mechanical ventilation, missing the opportunity for non-invasive treatment, and increasing the risk of complications and clinical deterioration. On the other hand, there are patients discharged from critical care units still in need of respiratory support, who are deprived of non-invasive therapies in the hospital ward. Furthermore, TNIs are the only option in those patients with orders not to intubate and in circumstances in which there is no possibility of admission to critical care units due to overcrowding. Given the risk of pathogen spread, many of these patients are being deprived of NITs.

TNIs have been widely used to treat patients with COVID-19 in China and have been shown to reduce intubation in patients with severe acute respiratory failure.[4] A panel of experts from 12 countries has recently published some guidelines that support the use of these therapies in COVID-19.[5] The available data tells us that TNIs should not be avoided, but rather applied in strict compliance with 3 requirements: (1) Do not delay intubation when necessary; (2) intensify protective measures, using the appropriate personal protection equipment and minimizing the aerosolization of particles by means of a specific assembly of masks and ventilation circuits; and (3) closely monitor these patients. We cannot afford to do without TNIs in the COVID-19 pandemic.

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Acute pancreatitis in a patient with COVID-19 infection☆

Pancreatitis aguda en paciente con infección por COVID-19

Dear Editor,

Since the first cases of the SARS-CoV-2 coronavirus infection appeared in the city of Wuhan, the disease has taken on pandemic characteristics. In Spain, according to the 14th May 2020 update from the Ministry of Health, there have been 228,540 cases, with a total of 27,321 deaths.

Although the severity of the infection is mainly determined by the development of severe pneumonia and acute respiratory *distress*, other conditions have been described in different organs and systems. Vomiting, diarrhoea and abdominal pain are common digestive system-related symptoms.[1] Liver involvement is also common.[2] We report a case of acute pancreatitis that could be related to COVID-19 infection.

A 76 year-old woman, ex-smoker, with low-risk alcohol consumption (10 g of pure alcohol, one day a week). Personal history of hypercholesterolemia and gastroesophageal reflux. Chronic

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omeprazole treatment (20 mg/day) for more than 10 years, which took on demand. Twenty-four days before hospital admission, the patient had taken three 500 mg tablets of azithromycin for acute sinusitis. She came to the hospital for an 8 h-history of epigastric pain, radiated to both hypochondriac regions, accompanied by vomiting. Approached as possible acute pancreatitis, it was confirmed by high levels of plasma amylase (3568 IU/L) and compatible abdominal ultrasound, without cholelithiasis. The rest of the laboratory parameters were normal, except for a slight increase of neutrophils (84%) and C-reactive protein (1.9 mg/dL). An abdominal CT confirmed the diagnosis and classified it as interstitial oedematous pancreatitis. A subsequent CT and magnetic resonance cholangiography showed similar findings and again ruled out biliary pathology. The PCR was positive for COVID-19, with symptoms of fever and diarrhoea. A chest X-ray was normal. Treatment with hydroxychloroquine, azithromycin, and lopinavir plus ritonavir was started, with a good response. Similarly, regarding the pancreatitis, the patient progressed favourably under conservative treatment.

We believe that the absence of at-risk alcohol consumption and calculous disease, the main causes of acute pancreatitis, point to a possible infectious cause of COVID-19. We do not believe that the history of taking azithromycin more than 3 weeks before is related to pancreatitis, which was not made worse by the reintroduction of azithromycin treatment. In this sense, a possible case of azithromycin-induced pancreatitis has been described in our setting, although the authors themselves stated that it was a difficult-to-demonstrate relationship.[2] Nor do we believe that omeprazole intake is the cause, since although cases[3] have been described, it is unlikely after 10 years of exposure. Both with azithromycin and omeprazole, the attribution of causality is doubtful with the Naranjo algorithm.

COVID-19-related pancreatic involvement has been described in the form of high amylase and lipase levels.[4] This involvement is pathophysiologically consistent, as the pancreas expresses the angiotensin-converting enzyme, whose receptors facilitate the penetration of the virus.[4] One case of acute pancreatitis attributable to COVID-19 infection has been described,[5] with compatible symptoms and CT scans, although no laboratory tests were available to demonstrate high levels of amylase. The patient had been diagnosed with COVID-19 infection and had received treatment with vancomycin and tetracycline, showing the symptoms compatible with acute pancreatitis 5 days after discharge. The latter antibiotic has also been linked to the development of acute pancreatitis.[3]

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Is it necessary to modify the clinical trials about osteoporosis? The serious problem of denosumab☆

¿Es necesario modificar los ensayos clínicos sobre osteoporosis? El grave problema de denosumab

Dear Editor,

The primary objective of randomized clinical trials for drugs used in the treatment of osteoporosis has been to reduce the risk of fracture, over and above changes in bone mineral density. Most of these trials, with few exceptions, have been carried out with a follow-up of 3 years. After confirming the effectiveness in reducing the risk of fracture, the drug follows the approval procedures by the corresponding agencies until its marketing.

However, so far, the design of clinical trials and, above all, the assessment of adverse effects has not taken into account what happens when drugs are discontinued. It is generally accepted that the drug stops working and that the patient goes back to his/her pre-treatment condition: for example, the discontinuation of a lipid-lowering treatment causes the slow and progressive elevation of serum lipid levels to values observed at treatment initiation.

In the field of osteoporosis, the most widely used pharmacological group, bisphosphonates, accumulate in bone tissue and this produces a beneficial residual effect in reducing the risk of fracture in such a way that, in the specific case of zoledronate, its administration for 6 consecutive years has a protective effect on the risk of fracture that lasts for 3 more years.[1] This has led to considering the discontinuation of bisphosphonate treatment after a few years of its administration, the so-called therapeutic holidays, which is a highly controversial topic.[2]

However, a very detrimental rebound effect has recently been found with a drug widely used in the treatment of osteoporosis, denosumab. And while it is true that while the drug is being administered there is a notable reduction in the risk of vertebral fracture (and much less in non-vertebral fractures), when denosumab is discontinued, a terrible rebound effect is observed, producing a sudden loss of bone mineral density, to the extent that the densitometric values are worse than at the beginning of the treatment[3] and, more seriously, up to 25% of patients have a vertebral fracture, which is often multiple,[4] not knowing the cause of this side effect and not being able to verify the efficacy of a treatment that avoids it, although the empirical use of an antiresorptive treatment is recommended.[3]

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